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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/40, 31/425, 31/445, 31/495,</b> <b>C07D 405/06, 487/16</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/29073</b> <b>(43) International Publication Date:</b> 26 September 1996 (26.09.96)
<b>(21) International Application Number:</b> PCT/US96/03611 <b>(22) International Filing Date:</b> 15 March 1996 (15.03.96) <b>(30) Priority Data:</b> 08/406,619 20 March 1995 (20.03.95) US 08/606,312 11 March 1996 (11.03.96) US <b>(60) Parent Applications or Grants</b> <b>(63) Related by Continuation</b> US 08/406,619 (CIP) Filed on 20 March 1995 (20.03.95) US 08/606,312 (CIP) Filed on 11 March 1996 (11.03.96) <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MEINKE, Peter, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHIH, Thomas [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FISHER, Michael, H. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(81) Designated States:</b> AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). <b>Published</b> With international search report.	
<b>(54) Title:</b> NODULISPORIC ACID DERIVATIVES			
<b>(57) Abstract</b>  The present invention relates to novel nodulisporic acid derivatives, which are acaricidal, antiparasitic, insecticidal and anthelmintic agents.			

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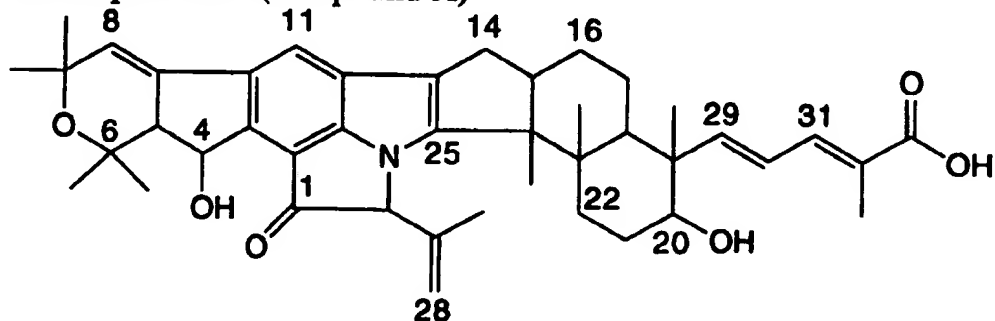
**TITLE OF THE INVENTION****NODULISPORIC ACID DERIVATIVES****CROSS REFERENCE**

- 5 This is a continuation-in part of co-pending application U.S.S.N. 08/406,619, filed March 20, 1995, which is hereby incorporated by reference.

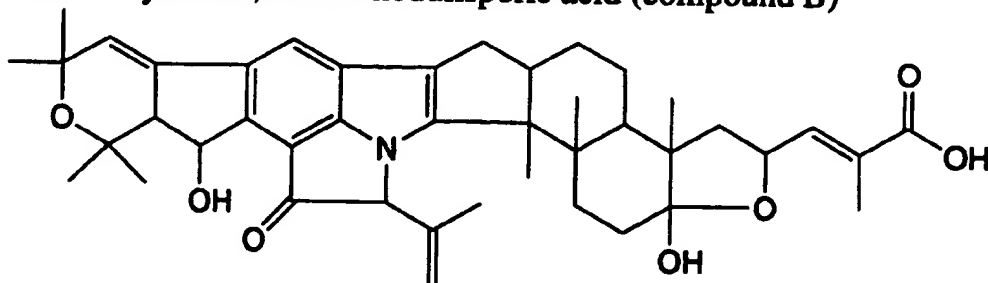
**BACKGROUND OF THE INVENTION**

- 10 Nodulisporic acid and two related components are antiparasitic agents and ectoparasitocidal agents isolated from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). These three compounds have the following structures:

- 15 nodulisporic acid (compound A)

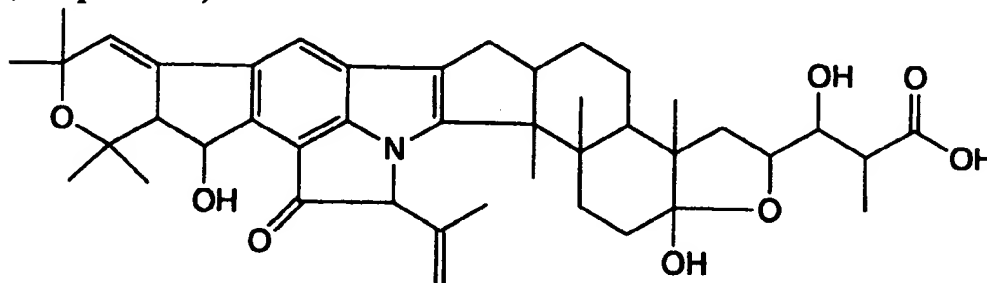


- 29,30-dihydro-20,30-oxa-nodulisporic acid (compound B)



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31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporic acid  
(compound C)

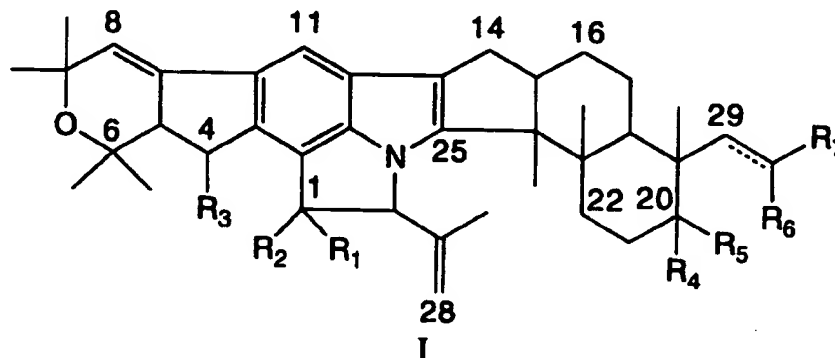


## 5 SUMMARY OF THE INVENTION

This invention relates to new acaricidal, antiparasitic, insecticidal and anthelmintic agents related to the nodulisporic acids, to processes for their preparation, compositions thereof, their use in the treatment of parasitic infections, including helminthiasis, in human and animals, and their use in the treatment of parasitic infections in plants or plant products.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:



20 wherein

- R<sub>1</sub> is
- (1) hydrogen,
  - (2) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
  - (3) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkenyl,

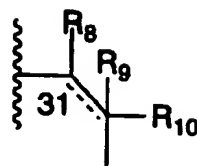


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- (4) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkynyl,  
 (5) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 (6) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 cycloalkyl and cycloalkenyl are 1 to 3 groups independently  
 selected from  
 (i) C<sub>1</sub>-C<sub>5</sub> alkyl,  
 (ii) X-C<sub>1</sub>-C<sub>10</sub> alkyl, where X is O or S(O)<sub>m</sub>.  
 (iii) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 (iv) hydroxy,  
 (v) halogen,  
 (vi) cyano,  
 (vii) carboxy,  
 (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are  
 independently H or C<sub>1</sub>-C<sub>10</sub> alkyl,  
 (ix) C<sub>1</sub>-C<sub>10</sub> alkanoylamino, and  
 (x) aroyl amino wherein said aroyl is  
 optionally substituted with 1 to 3 groups independently  
 selected from R<sup>f</sup>  
 (7) aryl C<sub>0</sub>-C<sub>5</sub> alkyl wherein said aryl is optionally  
 substituted with 1 to 3 groups independently selected from  
 R<sup>f</sup>,  
 (8) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl  
 (9) a 5- or 6-membered heterocycle containing from 1  
 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen atoms optionally substituted by 1 to 3 groups  
 independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>10</sub> alkyl  
 and halogen, and which may be saturated or partly  
 unsaturated,  
 R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are independently OR<sup>a</sup>, OCO<sub>2</sub>R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>; or  
 R<sub>1</sub>+R<sub>2</sub> represent =O, =NOR<sup>a</sup> or =N-NR<sup>c</sup>R<sup>d</sup>;  
 R<sub>5</sub> and R<sub>6</sub> are H; or  
 R<sub>5</sub> and R<sub>6</sub> together represent -O-;  
 R<sub>7</sub> is (1) CHO, or

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(2) the fragment



- |    |                    |      |   |
|----|--------------------|------|---|
|    | R <sub>8</sub> is  | (1)  | H,  |
|    |                    | (2)  | OR <sup>a</sup> , or                                    |
|    |                    | (3)  | NR <sup>c</sup> R <sup>d</sup>                          |
|    | R <sub>9</sub> is  | (1)  | H, or   |
| 5  |                    | (2)  | OR <sup>a</sup> ;                                       |
|    | R <sub>10</sub> is | (1)  | CN,   |
|    |                    | (2)  | C(O)OR <sup>b</sup> ,                                   |
|    |                    | (3)  | C(O)N(OR <sup>b</sup> )R <sup>c</sup> ,                 |
| 10 |                    | (4)  | C(O)NR <sup>c</sup> R <sup>d</sup> ,                    |
|    |                    | (5)  | NHC(O)OR <sup>b</sup> ,                                 |
|    |                    | (6)  | NHC(O)NR <sup>c</sup> R <sup>d</sup> ,                  |
|    |                    | (7)  | CH <sub>2</sub> OR <sup>a</sup> ,                       |
|    |                    | (8)  | CH <sub>2</sub> OCO <sub>2</sub> R <sup>b</sup> ,       |
|    |                    | (9)  | CH <sub>2</sub> OC(O)NR <sup>c</sup> R <sup>d</sup> ,   |
| 15 |                    | (10) | C(O)NR <sup>c</sup> NR <sup>c</sup> R <sup>d</sup> , or |
|    |                    | (11) | C(O)NR <sup>c</sup> SO <sub>2</sub> R <sup>b</sup> ;    |

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represents a single or a double bond;

- |    |                   |      |  |
|----|-------------------|------|--|
|    | R <sup>a</sup> is | (1)  | hydrogen,  |
|    |                   | (2)  | optionally substituted C <sub>1</sub> -C <sub>10</sub> alkyl,        |
| 20 |                   | (3)  | optionally substituted C <sub>3</sub> -C <sub>10</sub> alkenyl,      |
|    |                   | (4)  | optionally substituted C <sub>3</sub> -C <sub>10</sub> alkynyl,      |
|    |                   | (5)  | optionally substituted C <sub>1</sub> -C <sub>10</sub> alkanoyl,     |
|    |                   | (6)  | optionally substituted C <sub>3</sub> -C <sub>10</sub> alkenoyl,     |
|    |                   | (7)  | optionally substituted C <sub>3</sub> -C <sub>10</sub> alkynoyl,     |
| 25 |                   | (8)  | optionally substituted aroyl,  |
|    |                   | (9)  | optionally substituted aryl,   |
|    |                   | (10) | optionally substituted C <sub>3</sub> -C <sub>7</sub> cycloalkanoyl, |
|    |                   | (11) | optionally substituted C <sub>5</sub> -C <sub>7</sub> cycloalkenoyl, |
|    |                   | (12) | optionally substituted C <sub>1</sub> -C <sub>10</sub> alkylsulfonyl |

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- 5 (13) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl  
 (14) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl,  
 cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl  
 are from 1 to 10 groups independently selected from  
 hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl C<sub>1</sub>-C<sub>3</sub>  
 alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,  
 10 (15) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl,  
 (16) arylsulfonyl optionally substituted with 1 to 3  
 groups independently selected from C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub>  
 perfluoroalkyl, nitro, halogen and cyano,  
 15 (17) a 5- or 6-membered heterocycle containing 1 to 4  
 heteroatoms selected from oxygen, sulfur and nitrogen  
 optionally substituted by 1 to 4 groups independently  
 selected from C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkenyl, C<sub>1</sub>-C<sub>5</sub>  
 perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and  
 halogen, and which may be saturated or partly unsaturated;  
 R<sup>b</sup> is  
 20 (1) H,  
 (2) optionally substituted aryl,  
 (3) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,  
 (4) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkenyl,  
 (5) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkynyl,  
 25 (6) optionally substituted C<sub>3</sub>-C<sub>15</sub> cycloalkyl,  
 (7) optionally substituted C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, or  
 (8) optionally substituted 5- to 10-membered  
 heterocycle containing from 1 to 4 heteroatoms  
 independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
 cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 30 independently selected from  
 (i) hydroxy,  
 (ii) C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (iii) oxo,

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- 5 (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,  
 (v) aryl C<sub>1</sub>-C<sub>6</sub> alkoxy,  
 (vi) hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (vii) C<sub>1</sub>-C<sub>12</sub> alkoxy,  
 (viii) hydroxy C<sub>1</sub>-C<sub>6</sub> alkoxy,  
 (ix) amino C<sub>1</sub>-C<sub>6</sub> alkoxy,  
 (x) cyano,  
 (xi) mercapto,  
 10 (xii) C<sub>1</sub>-C<sub>6</sub> alkyl-S(O)<sub>m</sub>,  
 (xiii) C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted  
 with 1 to 4 groups independently selected from R<sup>e</sup>,  
 (xiv) C<sub>5</sub>-C<sub>7</sub> cycloalkenyl,  
 (xv) halogen,  
 (xvi) C<sub>1</sub>-C<sub>5</sub> alkanoyloxy,  
 15 (xvii) C(O)NR<sup>g</sup>R<sup>h</sup>,  
 (xviii) CO<sub>2</sub>R<sup>i</sup>,  
 (xix) formyl,  
 (xx) -NR<sup>g</sup>R<sup>h</sup>,  
 20 (xxi) 5 to 9-membered heterocycle, which may  
 be saturated or partially unsaturated, containing from 1 to 4  
 heteroatoms independently selected from oxygen, sulfur and  
 nitrogen, and optionally substituted with 1 to 5 groups  
 independently selected from R<sup>e</sup>,  
 25 (xxii) optionally substituted aryl, wherein the  
 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 independently selected from R<sup>e</sup>,  
 (xxiii) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from R<sup>e</sup>, and  
 30 (xxiv) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl;
- R<sup>c</sup> and R<sup>d</sup> are independently selected from R<sup>b</sup>; or  
 R<sup>c</sup> and R<sup>d</sup> together with the N to which they are attached form a 3- to 10-  
 membered ring containing 0 to 2 additional heteroatoms  
 selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1

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to 3 groups independently selected from R<sup>g</sup>, hydroxy, thioxo and oxo;

R<sup>e</sup> is

5

- (1) halogen,
- (2) C<sub>1</sub>-C<sub>7</sub> alkyl,
- (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (4) -S(O)<sub>m</sub>R<sup>i</sup>,
- (5) cyano,
- (6) nitro,
- (7) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
- (8) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
- (9) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,

10

(10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy,

15

(11) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>, or

(12) amino;

R<sup>f</sup> is

20

- (1) C<sub>1</sub>-C<sub>4</sub> alkyl,
- (2) X-C<sub>1</sub>-C<sub>4</sub> alkyl, where X is O or S(O)<sub>m</sub>,
- (3) C<sub>2</sub>-C<sub>4</sub> alkenyl,
- (4) C<sub>2</sub>-C<sub>4</sub> alkynyl,
- (5) C<sub>1</sub>-C<sub>3</sub>-perfluoroalkyl,
- (6) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl,

25

- (7) hydroxy,
- (8) halogen, and
- (9) C<sub>1</sub>-C<sub>5</sub> alkanoyl amino,

R<sup>g</sup> and R<sup>h</sup> are independently

30

- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>
- (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,

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- (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;
- (5) C<sub>1</sub>-C<sub>5</sub> alkoxy carbonyl,
- (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
- (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,
- (8) aryl C<sub>1</sub>-C<sub>5</sub> alkoxy carbonyl,
- (9) aminocarbonyl,
- (10) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl
- (11) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or
- (12) R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- R<sup>i</sup> is
- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (3) C<sub>1</sub>-C<sub>6</sub> alkyl,
- (4) optionally substituted aryl C<sub>0</sub>-C<sub>6</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy;
- m is 0 to 2; and
- v is 0 to 3; or
- a pharmaceutically acceptable salt thereof; and
- excluding nodulisporic acid, 29,30-dihydro-20,30-oxa-nodulisporic acid, and 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporic acid.

In a preferred embodiment, the present invention provides compounds of Formula I wherein

- R<sub>1</sub> is
- (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- (3) optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl,
- (4) optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl,
- (5) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl,

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- (6) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 cycloalkyl and cycloalkenyl are 1 to 3 groups independently  
 selected from
- (i) C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (ii) X-C<sub>1</sub>-C<sub>6</sub> alkyl, where X is O or S(O)<sub>m</sub>,
  - (iii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl,
  - (iv) hydroxy,
  - (v) halogen,
  - (vi) cyano,
  - (vii) carboxy, and
  - (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are  
 independently H or C<sub>1</sub>-C<sub>6</sub> alkyl,
- (7) aryl C<sub>0</sub>-C<sub>3</sub> alkyl wherein said aryl is optionally  
 substituted with 1 to 3 groups independently selected from  
 R<sup>f</sup>,
- (8) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (9) a 5- or 6-membered heterocycle containing from 1  
 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen atoms optionally substituted by 1 to 3 groups  
 independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl and  
 halogen, and which may be saturated or partly unsaturated,
- R<sub>8</sub> is
- (1) H,
  - (2) OH, or
- R<sub>9</sub> is
- (1) H or
  - (2) OH;
- R<sub>10</sub> is
- (1) C(O)OR<sup>b</sup>,
  - (2) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,
  - (3) C(O)NR<sup>c</sup>R<sup>d</sup>,
  - (4) NHC(O)OR<sup>b</sup>,
  - (5) NHC(O)NR<sup>c</sup>R<sup>d</sup>,
  - (6) CH<sub>2</sub>OR<sup>a</sup>,
  - (7) CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup>,

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- 5                      **R<sup>a</sup> is**  
                          (8)        CH<sub>2</sub>OC(O)NR<sup>c</sup>R<sup>d</sup>,  
                          (9)        C(O)NR<sup>c</sup>NR<sup>c</sup>R<sup>d</sup>, or  
                          (10)      C(O)NR<sup>c</sup>SO<sub>2</sub>R<sup>b</sup>;  
                          (1)        hydrogen,  
                          (2)        optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
                          (3)        optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,  
                          (4)        optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,  
                          (5)        optionally substituted C<sub>1</sub>-C<sub>6</sub> alkanoyl,  
 10                    (6)        optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenoyl,  
                          (7)        optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynoyl,  
                          (8)        optionally substituted aroyl,  
                          (9)        optionally substituted aryl,  
                          (10)      optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkanoyl,  
                          (11)      optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenoyl,  
 15                    (12)      optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl  
                          (13)      optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl  
                          (14)      optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl  
                          where the substituents on the alkyl, alkenyl, alkynyl,  
                          alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl,  
 20                    cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl  
                          are from 1 to 10 groups independently selected from  
                          hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, aryl C<sub>1</sub>-C<sub>3</sub>  
                          alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,  
                          (15)      C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 25                    (16)      arylsulfonyl optionally substituted with 1 to 3  
                          groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>  
                          perfluoroalkyl, halogen and cyano,  
                          (17)      a 5- or 6-membered heterocycle containing 1 to 4  
                          heteroatoms selected from oxygen, sulfur and nitrogen  
 30                    optionally substituted by 1 to 4 groups independently  
                          selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkenyl, C<sub>1</sub>-C<sub>3</sub>  
                          perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and  
                          halogen, and which may be saturated or partly unsaturated;  
                          **R<sup>b</sup> is**  
                          (1)        H,



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- 5 (2) optionally substituted aryl,  
 (3) optionally substituted C<sub>1</sub>-C<sub>7</sub> alkyl,  
 (4) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkenyl,  
 (5) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkynyl,  
 10 (6) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkyl,  
 (7) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, or  
 (8) optionally substituted 5- to 10-membered  
 heterocycle containing from 1 to 4 heteroatoms  
 independently selected from oxygen, sulfur and nitrogen;  
 15 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
 cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 independently selected from
- (i) hydroxy,
  - 15 (ii) C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (iii) oxo,
  - (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,
  - (v) aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,
  - (vi) hydroxy C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (vii) C<sub>1</sub>-C<sub>7</sub> alkoxy,
  - 20 (viii) hydroxy C<sub>1</sub>-C<sub>3</sub> alkoxy,
  - (ix) amino C<sub>1</sub>-C<sub>3</sub> alkoxy,
  - (x) cyano,
  - (xi) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (xii) C<sub>1</sub>-C<sub>3</sub> alkyl-S(O)<sub>m</sub>,
  - 25 (xiii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted  
 with 1 to 4 groups independently selected from R<sup>e</sup>,
  - (xiv) C<sub>5</sub>-C<sub>6</sub> cycloalkenyl,
  - (xv) halogen,
  - (xvi) C<sub>1</sub>-C<sub>3</sub> alkanoyloxy,
  - 30 (xvii) C(O)NR<sup>g</sup>R<sup>h</sup>,
  - (xviii) CO<sub>2</sub>R<sup>i</sup>,
  - (xix) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,
- wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R<sup>e</sup>,

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- (xx) -NR<sup>g</sup>R<sup>h</sup>,
- (xxi) 5 to 6-membered heterocycle, which may be saturated or partially unsaturated, containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 5 groups independently selected from R<sup>e</sup>, and
- (xxii) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R<sup>e</sup>;
- 10 R<sup>e</sup> is
- (1) halogen,
  - (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4) -S(O)<sub>m</sub>R<sup>i</sup>,
  - (5) cyano,
  - 15 (6) amino,
  - (7) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
  - (8) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
  - (9) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,
  - (10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or hydroxy, or
  - 20 (11) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>;
- R<sup>f</sup> is
- (1) methyl,
  - (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,
  - 25 (3) halogen,
  - (4) acetylamino,
  - (5) trifluoromethyl,
  - (6) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or methyl, and
  - 30 (7) hydroxy;
- R<sup>g</sup> and R<sup>h</sup> are independently
- (1) hydrogen,
  - (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>

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- (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;
- (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
- (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
- (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,
- (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
- (10) aminocarbonyl,
- (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl
- (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or

R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;

- R<sup>i</sup> is
- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (3) C<sub>1</sub>-C<sub>4</sub> alkyl,
- (4) optionally substituted aryl C<sub>0</sub>-C<sub>4</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and hydroxy;

all other variables are as defined under Formula I.

In another preferred embodiment, the present invention provides compounds of Formula I wherein

- R<sub>1</sub> is
- (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl,
- (3) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkenyl,
- (4) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkynyl,
- where the substituents on the alkyl, alkenyl, and alkynyl are 1 to 3 groups independently selected from
- (i) methyl,

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- (ii) X-methyl, where X is O or S(O)<sub>m</sub> and  
 (iii) halogen,  
 (5) aryl C<sub>0</sub>-C<sub>1</sub> alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from R<sup>f</sup>,
- 5 R<sup>g</sup> is (6) trifluoromethyl  
 (1) H,  
 (2) OH, or  
 (3) NH<sub>2</sub>
- 10 R<sup>9</sup> is (1) H, or  
 (2) OH;  
 R<sup>10</sup> is (1) C(O)OR<sup>b</sup>,  
 (2) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,  
 (3) C(O)NR<sup>c</sup>R<sup>d</sup>,  
 15 (4) NHC(O)OR<sup>b</sup>,  
 (5) NHC(O)NR<sup>c</sup>R<sup>d</sup>,  
 (6) CH<sub>2</sub>OR<sup>a</sup>,  
 (7) CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup>,  
 (8) CH<sub>2</sub>OC(O)NR<sup>c</sup>R<sup>d</sup>,  
 20 (9) C(O)NR<sup>c</sup>NR<sup>c</sup>R<sup>d</sup>, or  
 (10) C(O)NR<sup>c</sup>SO<sub>2</sub>R<sup>b</sup>;  
 R<sup>a</sup> is (1) hydrogen,  
 (2) optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl,  
 (3) optionally substituted C<sub>3</sub>-C<sub>4</sub> alkenyl,  
 25 (4) optionally substituted C<sub>3</sub>-C<sub>4</sub> alkynyl,  
 (5) optionally substituted C<sub>1</sub>-C<sub>4</sub> alkanoyl,  
 (6) optionally substituted aroyl,  
 (7) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkanoyl,  
 (8) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenoyl,  
 30 (9) optionally substituted C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl  
 where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, aroyl, cycloalkanoyl, cycloalkenoyl, and alkylsulfonyl, are from 1 to 5 groups independently selected

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from hydroxy, C<sub>1</sub>-C<sub>2</sub> alkoxy, aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,

(10) trifluoromethyl,

5 (11) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from methyl, trifluoromethyl and halogen,

(12) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from methyl, trifluoromethyl, C(O)NR<sup>c</sup>R<sup>d</sup>, CO<sub>2</sub>R<sup>b</sup> and halogen, and which may be saturated or partly unsaturated;

R<sup>b</sup> is

(1) H,  
(2) optionally substituted aryl,  
15 (3) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
(4) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,  
(5) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,  
(6) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
(7) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, or  
20 (8) optionally substituted 5- to 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen; where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

(i) hydroxy,  
(ii) C<sub>1</sub>-C<sub>3</sub> alkyl,  
(iii) oxo,  
(iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,  
30 (v) aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
(vi) hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl,  
(vii) C<sub>1</sub>-C<sub>4</sub> alkoxy,  
(viii) hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy,  
(ix) amino C<sub>1</sub>-C<sub>4</sub> alkoxy,

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- 5 (x) cyano,  
 (xi) C<sub>1</sub>-C<sub>4</sub> alkyl-S(O)<sub>m</sub>,  
 (xii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted  
 with 1 to 4 groups independently selected from R<sup>e</sup>,  
 (xiii) C<sub>5</sub>-C<sub>6</sub> cycloalkenyl,  
 (xiv) halogen,  
 (xv) C<sub>1</sub>-C<sub>3</sub> alkanoyloxy,  
 (xvi) C(O)NR<sup>g</sup>R<sup>h</sup>,  
 10 (xvii) CO<sub>2</sub>R<sup>i</sup>,  
 (xvii) -NR<sup>g</sup>R<sup>h</sup>,  
 (xix) 5 to 6-membered heterocycle, which may  
 be saturated or partially unsaturated, containing from 1 to 4  
 heteroatoms independently selected from oxygen, sulfur and  
 nitrogen, and optionally substituted with 1 to 5 groups  
 15 independently selected from R<sup>e</sup>,  
 (xx) optionally substituted aryl, wherein the  
 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 independently selected from R<sup>e</sup>,  
 (xxi) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 20 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from R<sup>e</sup>, and  
 (xxii) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl;  
 R<sup>e</sup> is  
 25 (1) halogen,  
 (2) C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (4) -S(O)<sub>m</sub>R<sup>i</sup>,  
 (5) cyano,  
 (6) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,  
 (7) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,  
 30 (8) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,  
 (9) optionally substituted aryl where the substituents  
 are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or  
 hydroxy,  
 (10) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>, or

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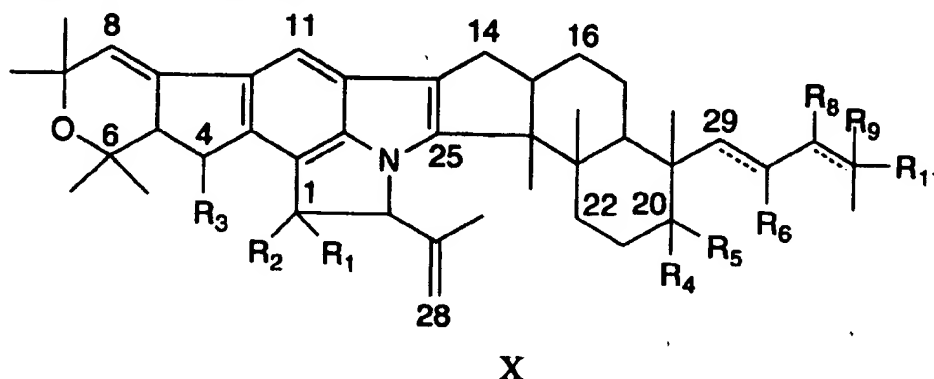
- 5  $R^f$  is  
 (11) amino;  
 (1) methyl,  
 (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 (3) trifluoromethyl,  
 (4) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or methyl,  
 (5) hydroxy,  
 (6) halogen, and  
 (7) acetylamino,
- 10  $R^g$  and  $R^h$  are independently  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>  
 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;  
 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,  
 (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (10) aminocarbonyl,  
 (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl  
 (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or
- 25  $R^g$  and  $R^h$  together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- 30  $R^i$  is  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (3) C<sub>1</sub>-C<sub>4</sub> alkyl,  
 (4) optionally substituted aryl C<sub>0</sub>-C<sub>6</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently

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selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy; and

all other variables are as defined under Formula I.

In another aspect of the present invention there are provided  
5 compounds having the formula X



where R<sub>1</sub> - R<sub>6</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined under formula I; and

- 10 R<sub>11</sub> is (1) COCl,  
(2) CON<sub>3</sub>, or  
(3) NCO.

Compounds of formula X are useful as intermediates in the  
preparation of certain compounds of formula I from Compounds A, B  
15 and C.

The present invention provides in another aspect  
pharmaceutical compositions comprising a compound of Formula I and a  
pharmaceutically acceptable carrier. Such compositions may further  
comprise one or more other active ingredients such as anthelmintic  
20 agents, insect regulators, ecdosyne agonists and fipronil.

The present invention provides in another aspect a method  
for treating parasitic diseases in a mammal which comprises  
administering an antiparasitic amount of a compound of Formula I. The  
treatment may further comprise co-administering one or more other  
25 active ingredients such as anthelmintic agents, insect regulators, ecdosyne  
agonists and fipronil.



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"Alkyl" as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert- butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as benzofused carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "heterocycle", unless otherwise specified, means mono- or bicyclic compounds that are saturated or partly unsaturated, as well as benzo- or heteroaromatic ring fused saturated heterocycles or partly unsaturated heterocycles, and containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen. Examples of saturated heterocycles include morpholine, thiomorpholine, piperidine, piperazine, tetrahydropyran, tetrahydrofuran, dioxane, tetrahydrothiophene, oxazolidine, pyrrolidine; examples of partly unsaturated heterocycles include dihydropyran, dihydropyridazine, dihydrofuran, dihydrooxazole, dihydropyrazole, dihydropyridine, dihydropyridazine and the like. Examples of benzo- or heteroaromatic ring fused heterocycle include 2,3-dihydrobenzofuranyl, benzopyranyl, tetrahydroquinoline, tetrahydroisoquinoline, benzomorpholinyl, 1,4-benzodioxanyl, 2,3-dihydrofuro(2,3-b)pyridyl and the like.

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The term "aryl" is intended to include mono- and bicyclic aromatic and heteroaromatic rings containing from 0 to 5 heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "aryl" is also meant to include benzofused cycloalkyl, benzofused cycloalkenyl, and benzofused heterocyclic groups. Examples of "aryl" groups include phenyl, pyrrolyl, isoxazolyl, pyrazinyl, pyridinyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidinyl, pyridazinyl, pyrazinyl, naphthyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furo(2,3-B)pyridyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, benzothiophenyl, quinolinyl, indolyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like.

Aroyl means arylcarbonyl in which aryl is as defined above.

Examples of  $\text{NR}^{\text{CRd}}$  or  $\text{NRGR}^{\text{h}}$  forming a 3- to 10-membered ring containing 0 to 2 additional heteroatoms selected from O,  $\text{S(O)}_{\text{m}}$  and N are aziridine, azetidine, pyrrolidine, piperidine, thiomorpholine, morpholine, piperazine, octahydroindole, tetrahydroisoquinoline and the like.

The term "optionally substituted" is intended to include both substituted and unsubstituted; thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus, for example,  $\text{OR}^{\text{a}}$  at C4 may represent OH and at C20 represent O-acyl.

Compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is intended to include all possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and all possible geometric isomers. In addition, the present invention includes all pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum,

ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Compounds of the present invention are named based on the trivial name of the parent compound, nodulisporic acid (compound A), and their position numbers are those as indicated in formula I.

Compounds of the present invention are prepared from the three nodulisporic acids (Compounds A, B and C), which in turn are obtained from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). The description of the producing microorganism, the fermentation process, and the isolation and purification of the three nodulisporic acids are disclosed in US Patent 5,399,582, issued March 21, 1995, which is hereby incorporated by reference in its entirety.

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The above structural formula is shown without a definitive stereochemistry at certain positions. However, during the the course of the synthetic procedures used to prepare such compounds, or using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers. In particular, the stereoisomers at C1, C4, C20, C26, C31 and C32 may be oriented in either the alpha- or beta-position, representing such groups oriented below or above the plane of the molecule, respectively. In each such case, and at other positions in the molecule, both the alpha- and beta-configurations are intended to be included within the ambit of this invention.

Compounds of formula I wherein the allyl group at position 26 is in the epi configuration may be obtained by treatment of the appropriate precursor with a bases such as hydroxide, methoxide, imidazole, triethylamine, potassium hydride, lithium diisopropylamide and the like in protic or aprotic solvents (as appropriate) such as water, methanol, ethanol, methylene chloride, chloroform, tetrahydrofuran, dimethylformamide and the like. The reaction is complete at temperatures from -78°C to the reflux temperature of the solution in from 15 minutes to 12 hours.

Compounds of formula I where R<sub>2</sub> (and R<sub>1</sub> is hydrogen), R<sub>3</sub>, R<sub>4</sub> and R<sub>8</sub> independently are hydroxy may be inverted by treatment of the appropriate alcohol using protocols known to those skilled in the art. For example, the alcohol may be reacted under Mitsunobu conditions with a carboxylic acid (formic acid, propionic acid, 2-chloroacetic acid, benzoic acid, para-nitro-benzoic acid and the like), a tri-substituted phosphine (triphenylphosphine, tri-n-butylphosphine, tripropylphosphine and the like) and a dialkyl diazodicarboxylate (diethyl diazodicarboxylate, dimethyl diazodicarboxylate, diisopropyl diazodicarboxylate and the like) in an aprotic solvent such as methylene chloride, tetrahydrofuran, chloroform, benzene and the like. The Mitsunobu reactions are complete in from 1 to 24 hours at temperatures from 0°C to the reflux temperature of the solution. The resultant esters may be hydrolyzed by treatment with hydroxide or ammonium hydroxide

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in a protic solvent such as methanol, ethanol, water, tetrahydrofuran/water or dimethylformamide/water and the like at from 0°C to the reflux temperature of the solution. Alternatively, the resultant esters may be hydrolyzed by treatment with a Lewis acid, such as  
5 magnesium chloride, aluminum chloride, titanium tetra-isopropoxide and the like in a protic solvent such as methanol, ethanol, isopropanol and the like and the reactions are complete in from 1 to 24 hours at 0°C to the reflux temperature of the solution.

During certain reactions described below, it may be  
10 necessary to protect the groups at R2, R3, R4, R8, R9 and R10. With these positions protected, the reactions may be carried out at other positions without affecting the remainder of the molecule. Subsequent to any of the described reactions (vida infra), the protecting group(s) may be removed and the unprotected product isolated. The protecting groups  
15 employed at R2, R3, R4, R8, R9 and R10 are those which may be readily synthesized, not significantly affected by the reactions at the other positions, and may be removed without significantly affecting any other functionality of the molecule. One preferred type of protecting group is the tri-substituted silyl group, preferably the tri-loweralkyl silyl group or  
20 di-loweralkyl-aryl silyl group. Especially preferred examples are the trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl and dimethylphenylsilyl groups.

The protected compound may be prepared with the appropriately substituted silyl trifluoromethanesulfonate or silyl halide,  
25 preferably the silyl chloride. The reaction is carried out in an aprotic solvent such as methylene chloride, benzene, toluene, ethyl acetate, isopropyl acetate, tetrahydrofuran, dimethylformamide and the like. In order to minimize side reactions, there is included in the reaction mixture a base to react with the acid released during the course of the reaction.  
30 Preferred bases are amines such as imidazole, pyridine, triethylamine or diisopropylethylamine and the like. The base is required in amounts equimolar to the amount of hydrogen halide liberated, however, generally several equivalents of the amine are employed. The reaction is stirred at

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from 0°C to the reflux temperature of the reaction mixture and is complete from 1 to 24 hours.

The silyl group is removed by treatment of the silyl compound with anhydrous pyridine-hydrogen fluoride in tetrahydrofuran or dimethylsulfoxide or with tetraalkylammonium fluoride in tetrahydrofuran. The reaction is complete in from 1 to 24 hours at from 0°C to 50°C. Alternatively, the silyl group may be removed by stirring the silylated compound in lower protic solvents such as methanol, ethanol, isopropanol and the like catalyzed by an acid, preferably a sulfonic acid monohydrate such as para-toluenesulfonic acid, benzenesulfonic acid or carboxylic acids such as acetic acid, propionic acid, monochloroacetic acid, dichloroacetic acid, trichloroacetic acid and the like. The reaction is complete in 1 to 24 hours at from 0°C to 50°C.

Protecting groups that may also be suitably used in the preparation of compounds of the present invention may be found in standard textbooks such as Greene and Wutz, Protective Groups in Organic Synthesis, 1991, John Wiley & Sons, Inc.

Compounds of formula I where R<sub>1</sub> and R<sub>2</sub> together represent an oxime, =NOR<sup>a</sup>, may be prepared by treating the appropriate oxo analog with H<sub>2</sub>NOR<sup>a</sup> to produce the corresponding oxime. Oxime formation may be accomplished using techniques known to those skilled in the art, including, but not restricted to, the use of H<sub>2</sub>NOR<sup>a</sup> either as the free base or as an acid addition salt such as the HCl salt, or an O-protected hydroxylamine such as O-trialkylsilylhydroxylamine, in a protic solvent such as methanol, ethanol, isopropanol and the like or aprotic solvents such as methylene chloride, chloroform, ethyl acetate, isopropyl acetate, tetrahydrofuran, dimethylformamide, benzene, toluene and the like, as appropriate. The reactions may be catalyzed by the addition of sulfonic acids, carboxylic acids or Lewis acids, including, but not limited to, benzenesulfonic acid monohydrate, para-toluenesulfonic acid monohydrate, acetic acid, zinc chloride and the like.

Similarly, compounds of formula I wherein R<sub>1</sub> and R<sub>2</sub> together represent =NNR<sup>c</sup>R<sup>d</sup> may be prepared by treating the appropriate

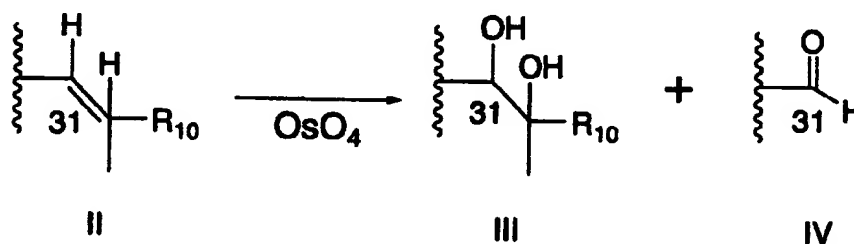
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oxo analog with  $H_2NNR^d$  to give the corresponding hydrazones using conditions directly analogous to those described for oxime formation.

Compounds of formula I wherein one or both of the  $---$  bonds represent a single bond may be prepared from the corresponding compound wherein  $---$  is a double bond by conventional hydrogenation procedures. The double bonds may be hydrogenated with any of a variety of standard precious metal hydrogenation catalysts such as Wilkinson's catalyst, Pearlman's catalyst, 1-25% palladium on carbon, 1-25% platinum on carbon and the like. The reaction is generally carried out in a non-reducible solvents (either protic or aprotic) such as methanol, ethanol, isopropanol, tetrahydrofuran, ethyl acetate, isopropyl acetate, benzene, toluene, dimethylformamide and the like. The hydrogen source may be hydrogen gas from 1 to 50 atmospheres of pressure or other hydrogen sources such as ammonium formate, cyclohexene, cyclohexadiene and the like. The reduction also may be carried out using sodium dithionite and sodium bicarbonate in the presence of a phase transfer catalyst, in particular a tetraalkylammonium phase transfer catalyst, and the like. The reactions may be run from  $0^\circ C$  to  $100^\circ C$  and are complete in from 5 min to 24 hours.

Compounds of formula I wherein  $R_8$  and  $R_9$  are both hydroxyl groups may be prepared according to the procedure shown in Scheme I.

# SCHEME I



Thus, Compound II is treated with osmium tetroxide under conditions known to those skilled in the art to yield the diol product III. Also produced during this reaction is the aldehyde IV. Osmium tetroxide may

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be used either stoichiometrically or catalytically in the presence of an oxidant, including, but not restricted to, morpholine N-oxide, trimethylamine N-oxide, hydrogen peroxide, tert-butyl hydroperoxide and the like. The dihydroxylation reactions may be performed in a variety  
5 of solvents or mixtures of solvents. These include both protic and aprotic solvents such as water, methanol, ethanol, tert-butanol, ether, tetrahydrofuran, benzene, pyridine, acetone and the like. The reactions may be performed at from -78°C to 80°C and are complete in from 5 minutes to 24 hours.

10           Compounds of formula I wherein R<sub>8</sub> is NR<sup>C</sup>R<sup>d</sup> and R<sub>9</sub> is hydrogen may be prepared by treatment of the appropriate precursor containing the C31-C32 unsaturation with HNR<sup>C</sup>R<sup>d</sup> or HCl•HNR<sup>C</sup>R<sup>d</sup> in an appropriate protic or aprotic solvents such as methanol, ethanol, benzene, toluene, dimethylformamide, dioxane, water and the like. The  
15 reaction may be facilitated by the addition of bases such as pyridine, triethylamine, sodium carbonate and the like or Lewis acids such as zinc chloride, magnesium chloride and the like. The reactions are complete in from 1 to 24 hours at temperatures from 0°C to the reflux temperature of the solution.

20           Compounds of formula I wherein R<sub>2</sub> is OH and R<sub>1</sub> is H may be prepared from the corresponding ketone by treating the appropriate oxo analog with standard reducing agents including, but not restricted to, sodium borohydride, lithium borohydride, lithium aluminum hydride, potassium tri-sec-butyl borohydride, diisobutylaluminum hydride,  
25 diborane oxazaborolidines and alkylboranes (both achiral and chiral). These reactions are performed in a manner known to those skilled in the art and are carried out in non-reducible solvents such as methanol, ethanol, diethyl ether, tetrahydrofuran, hexanes, pentane, methylene chloride and the like. The reactions are complete in from 5 minutes to 24  
30 hours at temperatures ranging from -78°C to 60°C. Compounds of formula I wherein R<sub>2</sub> is OH, R<sub>1</sub> is H and R<sub>10</sub> is CH<sub>2</sub>OH may be obtained by reacting the appropriate carboxylic acid or ester analog (e.g., where R<sub>10</sub> is CO<sub>2</sub>H or CO<sub>2</sub>R<sup>a</sup>) with the more reactive reducing agents as described above, including lithium aluminum hydride, lithium



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borohydride and the like. Compounds of formula I wherein R<sub>2</sub> and R<sub>1</sub> together are oxo and R<sub>10</sub> is CH<sub>2</sub>OH may be obtained by reacting the appropriate carboxylic acid (e.g., where R<sub>10</sub> is CO<sub>2</sub>H) with less reactive reducing agents such as diborane and the like.

- 5           Compounds of formula I wherein R<sub>2</sub> is OH and R<sub>1</sub> is other than H, may be prepared from the corresponding ketone by treating the appropriate oxo analog with a Grignard reagent R<sub>1</sub>MgBr, or with a lithium reagent R<sub>1</sub>Li. These reactions are performed in a manner known to those skilled in the art and preferably are performed in aprotic solvents  
10 such as diethyl ether, tetrahydrofuran, hexanes or pentanes. The reactions are complete in from 5 minutes to 24 hours at temperatures ranging from -78°C to 60°C.

- Compounds of formula I where R<sub>10</sub> is C(O)N(OR<sup>b</sup>)R<sup>c</sup> or C(O)NR<sup>c</sup>R<sup>d</sup> are prepared from the corresponding carboxylic acid using  
15 standard amide-forming reagents known to those skilled in the art. The reaction is carried out using at least one equivalent of an amine nucleophile, HN(OR<sup>b</sup>)R<sup>c</sup> or HNR<sup>c</sup>R<sup>d</sup>, although preferably ten to one hundred equivalents of amine nucleophiles are employed. Amide-forming reagents include, but are not restricted to,  
20 dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl), diisopropylcarbodiimide, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium  
25 hexafluorophosphate (PyBOP), chloro-tris-pyrrolidino-phosphonium hexafluorophosphate (PyCloP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), diphenylphosphoryl azide (DPPA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazol-1-yl-N,N,N',N'-bis(pentamethylene)uronium  
30 hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The amide-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole or N-hydroxy-7-aza-benzotriazole. The amidation reaction is generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as

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triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaminopyridine and the like. The carboxyl group may be activated for amide bond formation via its corresponding acid chloride or mixed anhydride, using conditions known to those skilled in the art.

- 5 These amide-forming reactions are carried out in aprotic solvents such as methylene chloride, tetrahydrofuran, diethyl ether, dimethylformamide, N-methylpyrrolidine and the like at -20°C to 60°C and are complete in 15 minutes to 24 hours.

- Compounds of formula I where R<sub>10</sub> is cyano may be prepared by treatment of the appropriate carboxamide with dehydrating reagents known to those skilled in the art such as para-toluenesulfonyl chloride, methanesulfonyl chloride, acetyl chloride, thionyl chloride, phosphorus oxychloride or catecholboron chloride in an aprotic solvent such as methylene chloride, chloroform, tetrahydrofuran, benzene, toluene and the like. The reactions are complete in from 15 minutes to 24 hours at temperatures from -78°C to the reflux temperature of the solution.

- Compounds of formula I where R<sub>10</sub> is C(O)OR<sup>b</sup> are prepared from the corresponding carboxylic acid using standard ester-forming reagents known to those skilled in the art. The esterification reaction is carried out using at least one equivalent of an alcohol, HOR<sup>b</sup>, although preferably ten to one hundred equivalents of alcohol are used; the esterification also may be carried out using the alcohol as solvent. Esterification reagents include, but are not restricted to, dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl), diisopropylcarbodiimide, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), chloro-tris-pyrrolidino-phosphonium hexafluorophosphate (PyCloP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), diphenylphosphoryl azide (DPPA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazol-1-yl-N,N,N',N'-bis(pentamethylene)uronium

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- hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The ester-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole, N-hydroxy-7-aza-benzotriazole, 4-(N,N-dimethylamino)pyridine or 4-pyrrolidinopyridine. The reaction is
- 5 generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as triethylamine, diisopropylethylamine, pyridine and the like. The carboxyl group may be activated for ester bond formation via its corresponding acid chloride or mixed anhydride, using conditions known to those skilled in the art.
- 10 These ester-forming reactions are carried out in aprotic solvents such as methylene chloride, tetrahydrofuran, diethyl ether, dimethylformamide, N-methylpyrrolidine and the like at temperatures ranging from -20°C to 60°C and are complete in 15 minutes to 24 hours.

- Compounds of formula I wherein one or more of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub> and R<sub>9</sub> is OR<sup>a</sup>, OCO<sub>2</sub>R<sup>b</sup> or OC(O)NR<sup>c</sup>R<sup>d</sup>, and/or where R<sub>10</sub> is CH<sub>2</sub>OR<sup>a</sup>, CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup> or CH<sub>2</sub>OC(O)NR<sup>c</sup>R<sup>d</sup> may be prepared using known methods for acylation, sulfonylation and alkylation of alcohols. Thus, acylation may be accomplished using reagents such as acid
- 15 anhydrides, acid chlorides, chloroformates, carbamoyl chlorides, isocyanates and amine bases according to general procedures known to those skilled in the art. Sulfonylations may be carried out using sulfonylchlorides or sulfonic anhydrides. The acylation and sulfonylation reactions may be carried out in aprotic solvents such as methylene chloride, chloroform, pyridine, benzene, toluene and the like. The
- 20 acylation and sulfonylation reactions are complete in from 15 minutes to 24 hours at temperatures ranging from -20°C to 80°C. The degree of acylation, sulfonylation and alkylation will depend on the amount of the reagents used. Thus, for example, using one equivalent of an acylating reagent and one equivalent of nodulisporic acid results in a product
- 25 mixture containing 4- and 20-acylated nodulisporic acid; such a mixture may be separated by conventional techniques such as chromatography.
- 30

Compounds of formula I wherein one or more of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub> and R<sub>9</sub> is OR<sup>a</sup> and/or where R<sub>10</sub> is CH<sub>2</sub>OR<sup>a</sup>, may be prepared using methods known to those skilled in the art for the alkylation of

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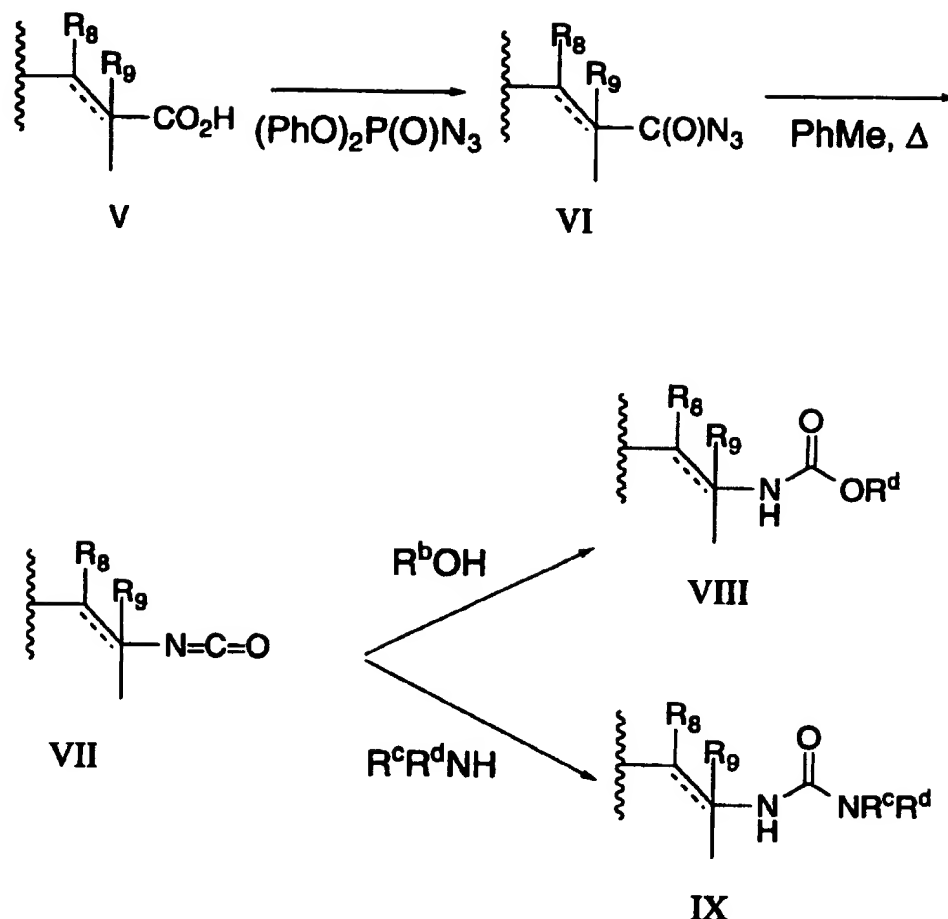
alcohols. Thus, alkylation may be accomplished using reagents including, but not restricted to, halides  $IR^a$ ,  $BrR^a$ ,  $ClR^a$ , diazo reagents  $N_2R^a$ , trichloroacetimidates  $R^aOC(NH)CCl_3$ , sulfates  $R^aOSO_2Me$ ,  $R^aOSO_2CF_3$ , and the like. The alkylation reactions may be facilitated by the addition of acid, base or Lewis acids, as appropriate. The reactions are performed in aprotic solvents such as methylene chloride, chloroform, tetrahydrofuran, benzene, toluene, dimethylformamide, N-methylpyrrolidine, dimethyl sulfoxide, hexamethylphosphoramide and are complete at from  $0^\circ C$  to the reflux temperature of the solution from 15 minutes to 48 hours.

Compounds of formula I where  $R_{10}$  is  $NHC(O)OR^b$  or  $C(O)NR^cR^d$  are prepared from the corresponding carboxylic acid via the corresponding acyl azide (VI) and isocyanate (VII) as shown in Scheme II.

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## SCHEME II



- 5 In Scheme II,  $\text{R}_8$ ,  $\text{R}_9$ ,  $\text{R}^b$ ,  $\text{R}^c$ ,  $\text{R}^d$  and ---- have the same meaning as defined under formula I. Thus, the carboxylic acid (compound V) is treated with diphenylphosphoryl azide to provide the acyl azide (compound VI). Heating of compound VI in an aprotic solvent such as benzene, toluene, dimethylformamide and the like results in a rearrangement yielding compound VII, an isocyanate. Compound VII may be reacted in an aprotic solvent such as benzene, toluene, methylene chloride, 1,2-dichloroethylene, dimethylformamide and the like, with an alcohol  $\text{R}^b\text{OH}$ , such as methanol, ethanol, benzyl alcohol, 2-trimethylsilylethanol, 2,2,2-trichloroethanol, methyl glycolate, phenol and the like to yield compound VIII, a carbamate. The addition of one or
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more equivalents of an amine base such as triethylamine, diisopropylethylamine, pyridine and the like may be employed to accelerate carbamate formation. The carbamate-forming reactions may be performed from 0°C to 100°C and are complete in 15 minutes to 24 hours.

Compounds of formula IX may be prepared when compounds of formula VII are reacted with an appropriate amine  $\text{HNR}^c\text{R}^d$  in an aprotic solvent such as methylene chloride, tetrahydrofuran, dimethylformamide, dimethylsulfoxide, benzene, toluene and the like. The urea-forming reactions may be performed from 0°C to 100°C and are complete in 15 minutes to 24 hours.

The instant compounds are potent endo- and ecto-antiparasitic agents against parasites particularly helminths, ectoparasites, insects, and acarides, infecting man, animals and plants, thus having utility in human and animal health, agriculture and pest control in household and commercial areas.

The disease or group of diseases described generally as helminthiasis is due to infection of an animal host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats, fish, buffalo, camels, llamas, reindeer, laboratory animals, furbearing animals, zoo animals and exotic species and poultry. Among the helminths, the group of worms described as nematodes causes widespread and often times serious infection in various species of animals. The most common genera of nematodes infecting the animals referred to above are *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Chabertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*, *Habronema*, *Druschia*, *Heterakis*, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. Certain of these, such as *Nematodirus*, *Cooperia*, and *Oesophagostomum* attack primarily the intestinal tract while others, such as *Haemonchus* and *Ostertagia*, are more prevalent in the stomach while still others such as *Dictyocaulus* are found in the lungs. Still other parasites may be located in other tissues

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and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs and, if left untreated, may result in death of the infected host. The compounds of this invention have activity against these parasites, and in addition are also active against *Dirofilaria* in dogs and cats, *Nematospiroides*, *Syphacia*, *Aspiculuris* in rodents, arthropod ectoparasites of animals and birds such as ticks, mites such as scabies lice, fleas, blowflies, and other biting insects in domesticated animals and poultry, such as *Tenophalides*, *Ixodes*, *Psoroptes*, and *Hemotobia*, in sheep *Lucilia* sp., biting insects and such migrating dipterous larvae as *Hypoderma* sp. in cattle, *Gastrophilus* in horses, and *Cuterebra* sp. in rodents and nuisance flies including blood feeding flies and filth flies.

The instant compounds are also useful against parasites which infect humans. The most common genera of parasites of the gastro-intestinal tract of man are *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris*, and *Enterobius*. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filarial worms such as *Wuchereria*, *Brugia*, *Onchocerca* and *Loa*, *Dracunculus* and extra intestinal stages of the intestinal worms *Strongyloides* and *Trichinella*. The compounds are also of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

The compounds are also active against household pests such as the cockroach, *Blatella* sp., clothes moth, *Tineola* sp., carpet beetle, *Attagenus* sp., the housefly *Musca domestica* as well as fleas, house dust mites, termites and ants.

The compounds are also useful against insect pests of stored grains such as *Tribolium* sp., *Tenebrio* sp. and of agricultural plants such as aphids, (*Acyrtosiphon* sp.); against migratory orthopterans such as locusts and immature stages of insects living on plant tissue. The compounds are useful as a nematocide for the control of soil nematodes

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and plant parasites such as *Meloidogyne* sp. which may be of importance in agriculture. The compounds are also highly useful in treating acreage infested with fire ant nests. The compounds are scattered above the infested area in low levels in bait formulations which are brought back to the nest. In addition to a direct-but-slow onset toxic effect on the fire ants, the compound has a long-term effect on the nest by sterilizing the queen which effectively destroys the nest.

The compounds of this invention may be administered in formulations wherein the active compound is intimately admixed with one or more inert ingredients and optionally including one or more additional active ingredients. The compounds may be used in any composition known to those skilled in the art for administration to humans and animals, for application to plants and for premise and area application to control household pests in either a residential or commercial setting. For application to humans and animals to control internal and external parasites, oral formulations, in solid or liquid or parenteral liquid, implant or depot injection forms may be used. For topical application dip, spray, powder, dust, pour-on, spot-on, jetting fluid, shampoos, collar, tag or harness, may be used. For agricultural premise or area application, liquid spray, powders, dust, or bait forms may be used. In addition "feed-through" forms may be used to control nuisance flies that feed or breed in animal waste. The compounds are formulated, such as by encapsulation, to leave a residue of active agent in the animal waste which controls filth flies or other arthropod pests.

These compounds may be administered orally in a unit dosage form such as a capsule, bolus or tablet, or as a liquid drench where used as an anthelmintic in mammals. The drench is normally a solution, suspension or dispersion of the active ingredient usually in water together with a suspending agent such as bentonite and a wetting agent or like excipient. Generally, the drenches also contain an antifoaming agent. Drench formulations generally contain from about 0.001 to 0.5% by weight of the active compound. Preferred drench formulations may contain from 0.01 to 0.1% by weight. The capsules and



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boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate.

Where it is desired to administer the instant compounds in a dry, solid unit dosage form, capsules, boluses or tablets containing the  
5 desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents, and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be  
10 varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top  
15 dressing or in the form of pellets or liquid which may then be added to the finished feed or optionally fed separately. Alternatively, feed based individual dosage forms may be used such as a chewable treat. Alternatively, the antiparasitic compounds of this invention may be administered to animals parenterally, for example, by intraruminal,  
20 intramuscular, intravascular, intratracheal, or subcutaneous injection in which the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral  
25 vehicles such as organic preparation using solketal, glycerol formal, propylene glycol, and aqueous parenteral formulations are also used. The active compound or compounds are dissolved or suspended in the parenteral formulation for administration; such formulations generally contain from 0.0005 to 5% by weight of the active compound.

30 The agents of this invention can be used in the treatment and/or prevention of diseases caused by parasites, for example, arthropod parasites such as ticks, lice, fleas, mites and other biting arthropods in domesticated animals and poultry. The agents of this invention also are useful in the prevention and treatment of diseases caused by

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helminthiasis. They are also effective in treatment of parasitic diseases that occur in other animals including humans. The optimum amount to be employed for best results will, of course, depend upon the particular compound employed, the species of animal to be treated and the type and severity of parasitic infection or infestation. Generally good results are obtained with our novel compounds by the oral administration of from about 0.001 to 500 mg per kg of animal body weight, such total dose being given at one time or in divided doses over a relatively short period of time such as 1-5 days. With the preferred compounds of the invention, excellent control of such parasites is obtained in animals by administering from about 0.025 to 100 mg per kg of body weight in a single dose. Repeat treatments are given as required to combat re-infections and are dependent upon the species of parasite and the husbandry techniques being employed. Repeat treatments may be given daily, weekly, biweekly or monthly, or any combination thereof, as required. The techniques for administering these materials to animals are known to those skilled in the veterinary field.

When the compounds described herein are administered as a component of the feed of the animals, or dissolved or suspended in the drinking water, compositions are provided in which the active compound or compounds are intimately dispersed in an inert carrier or diluent. By inert carrier is meant one that will not react with the antiparasitic agent and one that may be administered safely to animals. Preferably, a carrier for feed administration is one that is, or may be, an ingredient of the animal ration.

Suitable compositions include feed premixes or supplements in which the active ingredient is present in relatively large amounts and which are suitable for direct feeding to the animal or for addition to the feed either directly or after an intermediate dilution or blending step. Typical carriers or diluents suitable for such compositions include, for example, distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, wheat shorts, molasses solubles, corn cob meal, edible bean mill feed, soya grits, crushed limestone and the like. The active compounds are intimately dispersed throughout the carrier by

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methods such as grinding, stirring, milling or tumbling. Compositions containing from about 0.005 to 2.0% weight of the active compound are particularly suitable as feed premixes. Feed supplements, which are fed directly to the animal, contain from about 0.0002 to 0.3% by weight of the active compounds.

Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment and control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular compound employed, the compounds of this invention are usually fed at concentrations of between 0.00001 to 0.002% in the feed in order to achieve the desired anti-parasitic result.

In using the compounds of this invention, the individual compounds may be prepared and used in that form. Alternatively, mixtures of the individual compounds may be used, or they may be combined with other active compounds not related to the compounds of this invention.

The compounds of this invention are also useful in combatting agricultural pests that inflict damage upon crops while they are growing or while in storage. The compounds are applied using known techniques as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from such agricultural pests.

Compounds of this invention may be co-administered with anthelmintic agents. These anthelmintic agents are meant to include, but not be restricted to, compounds selected from the avermectin and milbemycin class of compounds such as ivermectin, avermectin, abamectin, emamectin, eprinamectin, doramectin, fulladectin, moxidectin, Interceptor and nemadectin. Additional anthelmintic agents include the benzimidazoles such as thiabendazole, cambendazole, parbendazole, oxibendazole, mebendazole, flubendazole, fenbendazole, oxfendazole, albendazole, cyclobendazole, febantel, thiophanate and the like. Additional anthelmintic agents include imidazothiazoles and

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tetrahydropyrimidines such as tetramisole-levamisole, butamisol, pyrantel, pamoate, aoxantel or morantel.

Compounds of this invention may be co-administered with fipronil.

5           Compounds of this invention may be co-administered with an insect growth regulator with molt inhibiting activity such as lufenuron and the like.

          Compounds of this invention may be co-administered with ecdysone agonist such as tebufenozide and the like, which induces  
10 premature molt and causes feeding to cease.

The co-administered compounds are given via routes, and in doses, that are customarily used for those compounds.

          Also included in the present invention are pharmaceutical compositions containing a compound of the present invention in  
15 combination with an anthelmintic agent, fipronil, an insect growth regulator, or a ecdysone agonist.

The following examples are provided to more fully illustrate the present invention, and shall not be construed as limiting the scope in any manner.

20

#### EXAMPLE 1

##### Methyl nodulisporate

          To 5.4 mg nodulisporic acid in 5 mL methanol at room  
25 temperature was added 0.5 mL 10% trimethylsilyldiazomethane in hexanes. After 15 minutes, three drops of glacial acetic acid was added and the solution diluted with benzene, frozen and lyophilized. Pure methyl ester was obtained following reversed-phase HPLC purification using 85:15 methanol:water as eluant and the product was characterized  
30 by <sup>1</sup>H NMR and mass spectrometry.

#### EXAMPLE 2

##### Methyl 29,30-dihydro-20,30-oxa-nodulisporate

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To 0.8 mg Compound B in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated NaHCO<sub>3</sub> was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

10

## EXAMPLE 3

Methyl 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydronodulisporate

To 1 mg Compound C in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated NaHCO<sub>3</sub> was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 17.5:82.5 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

20

## EXAMPLE 4

Ethyl nodulisporate

To a solution containing 20 mg nodulisporic acid in 2 mL methylene chloride at room temperature was added 0.11 mL ethanol, 0.008 mL diisopropylethylamine, 1 mg N,N-dimethylaminopyridine (DMAP) followed by 13 mg BOP reagent. After 50 hours at room temperature, the solution was poured into 1/1 saturated sodium bicarbonate/brine and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, the solids were removed by filtration and the solution concentrated under reduced pressure. Pure product was obtained following preparative TLC on silica gel (one 1000 micron plate) using 1/3 acetone/hexanes as eluant. Purified product (15

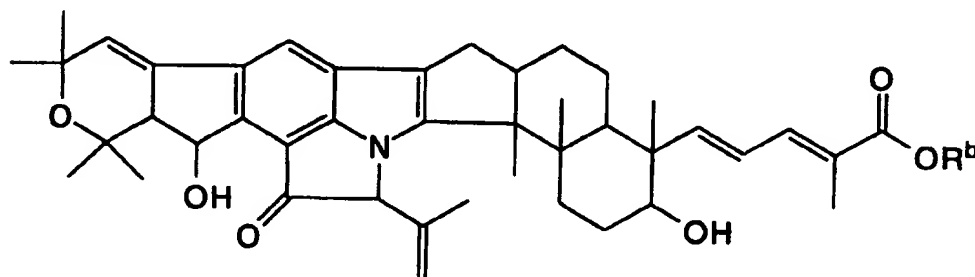
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- 40 -

mg) was characterized by proton NMR and mass spectrometry ( $m/z$ : 708.4 ( $M+1$ )).

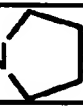
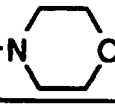
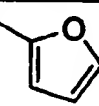
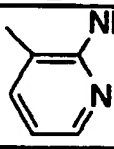
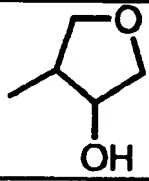
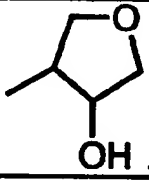
- 5 The general procedure of Example 4 was repeated using the alcohols listed in Table 1 below to provide the corresponding nodulisporate derivatives. These compounds were characterized by proton NMR and/or mass spectrometry ( $m/z$  is for ( $M+1$ ) unless otherwise specified).

10 Table 1: Ester Derivatives of Nodulisporic Acid



Ex.	$m/z$	Alcohol	R <sup>b</sup>
5	797.6	N-Hydroxybenzotriazole	
6	724.4	2-Hydroxyethanol	CH <sub>2</sub> CH <sub>2</sub> OH
7	807.5	2-(Diisopropylamino)-ethanol	CH <sub>2</sub> CH <sub>2</sub> N(CH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>2</sub>
8	738.4	3-Hydroxypropanol	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH
9	752.3	4-Hydroxybutanol	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH
10	767.0	5-Hydroxypentanol	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH
11	751.5	2-Dimethylaminoethanol	CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>
12	837.7	3-Diisopropylamino-2-hydroxypropanol	CH <sub>2</sub> CH(OH)CH <sub>2</sub> N(CH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>2</sub>
13	768.9	2-(2-Hydroxyethoxy)-ethanol	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> OH

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14	815.4	4-Nitrobenzyl alcohol	CH <sub>2</sub> Ph(4-NO <sub>2</sub> )
15	815.4	3-Nitrobenzyl alcohol	CH <sub>2</sub> Ph(3-NO <sub>2</sub> )
16	807.7	2-Hydroxy-3-(1-pyrrolidinyl)propanol	CH <sub>2</sub> CH(OH)CH <sub>2</sub> -N 
17	793.7	4-(2-Hydroxyethyl)-morpholine	CH <sub>2</sub> CH <sub>2</sub> — N 
18	762.4	2,2,2-Trifluoroethanol	CH <sub>2</sub> CF <sub>3</sub>
19		2-(Hydroxymethyl)furan	CH <sub>2</sub> 
20	764.5	5-Hydroxypentan-2-one	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> C(=O)CH <sub>3</sub>
21		3-Phenylpropanol	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Ph
22	764.3	3,3-Dimethylbutanol	CH <sub>2</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>3</sub>
23		2-(N-Acetylamino)-3-hydroxypyridine	
24	766.7	3,4-Dihydroxytetrahydrofuran, Isomer A	 OH, isomer A
25	766.6	3,4-Dihydroxytetrahydrofuran, Isomer B	 OH, isomer B
26	831.5	1,1,1,3,3,3-hexafluoroisopropanol	CH(CF <sub>3</sub> ) <sub>2</sub>
27		2-(Trifluoromethyl)benzyl alcohol	CH <sub>2</sub> Ph(2-CF <sub>3</sub> )

## EXAMPLE 28

General Procedure for the Preparation of Additional Ester Derivatives of Compounds A, B and C

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To a solution containing 20 mg Compound A, B or C in 2 mL methylene chloride at room temperature add 110 mg of an alcohol selected from Table 2, 0.008 mL diisopropylethylamine and 1 mg DMAP followed by 13 mg BOP reagent. After from 1 hour to 3 days at room temperature, pour the solution into 1/1 saturated sodium bicarbonate/brine and extract with methylene chloride. The combined organic layers may be dried over sodium sulfate and the solids may be removed by filtration. Concentrate the solution under reduced pressure. Pure product may be obtained following flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography. Purified product may be characterized by proton NMR and/or mass spectrometry.

Table 2: Alcohols for the Preparation of Additional Ester Derivatives of Compounds A, B and C

3-(Methylthio)propanol, 1H,1H-Pentafluoropropanol, 2-Pentyn-1-ol, 3-Pentyne-1-ol, 4-Pentyne-1-ol, Propanol, 2-Hydroxyethanol, Methyl glycolate, Glycolic acid, 4-(Methoxy)benzyl alcohol, 3-(Dimethylamino)propanol, 3-(4-Morpholinyl)propanol, 2-(Hydroxymethyl)pyridine, 1-(2-Hydroxyethyl)piperazine, 2-Hydroxy-3-phenylpropanol, 2-(Hydroxyethoxy)ethanol, 4-(2-Hydroxyethyl)morpholine, 1-(2-Hydroxyethyl)piperidine, 3-(Hydroxymethyl)pyridine, 1-(Hydroxymethyl)pyrimidine, 3-Hydroxypropanol, 4-Hydroxybutanol, 1-(2-Hydroxyethyl)-4-methylpiperazine, 2-(2-Hydroxyethyl)pyridine, 1-(3-Hydroxypropyl)-2-pyrrolidinone, 1-(2-Hydroxyethyl)pyrrolidine, 1-(3-Hydroxypropyl)imidazole, 2-Hydroxybutanol, 4-(Hydroxymethyl)pyridine, 2-Hydroxypyrazine, Hydroxyacetonitrile, 6-Hydroxyhexanol, 4-(3-Hydroxypropyl)morpholine, 2-Hydroxypropanol, 2-Hydroxypentanol, 1-Hydroxy-1-(hydroxymethyl)cyclopentane, 2-(Methylthio)ethanol, 3-Hydroxy-1,2,4-triazine, 2-Amino-3-hydroxypyridine, 2-(Ethylthio)ethanol, Glycolamide, 2-Hydroxy-2-



- (hydroxymethyl)propanol, trans-2-Hydroxycyclohexanol, 2-Hydroxy-4-methylphenol, 2-(Hydroxymethyl)pyridine, 1-Hydroxymethyl-1-cyclohexanol, 2-Hydroxyhexanol, 2-Hydroxy-1-methoxypropane, 2-(Hydroxymethyl)imidazole, 3-Hydroxymethylpyrazole, trans-4-
- 5 Hydroxycyclohexanol, N-Acetyl-4-hydroxybutylamine, Hydroxycyclopentane, 2-(Methylsulfonyl)ethanol, 2-(Methylsulfinyl)ethanol, 4-(2-Hydroxyethyl)phenol, 2-(2-Hydroxyethyl)phenol, 2-Hydroxy-3-methylbutanol, 3-(N-Acetylamino)propanol, 3-(Diethylamino)propanol, 3-
- 10 (Dimethylamino)propanol, Allyl alcohol, 2-(Dimethylamino)ethanol, Glycerol, 2-Methoxyethanol, 2-(N-Acetylamino)ethanol, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrrolidine, 2-(Hydroxyethyl)benzene, 2-Hydroxyethyl-1-methylpyrrolidine, 2-Hydroxy-2-methyl-propanol, Cyclopropanol, Cyclohexanol, 3-
- 15 Hydroxypropanol, 3-Ethoxypropanol, Propargyl alcohol, Ethyl glycolate, 2-Fluoroethanol, 3-(Dodecyloxy)propanol, 4-Hydroxybutanol, 5-Hydroxypentanol, 2-(Dimethylamino)ethanol, 2-(2-Hydroxyethoxy)ethanol, 1-(2-Hydroxyethyl)imidazolone, 2-(2-Hydroxyethoxy)ethylamine, Isopropanol, 2,2,2-Trifluoroethanol, 4-
- 20 Nitrobenzyl alcohol, 3-Nitrobenzyl alcohol, 2-Methoxyethanol, 4-(Hydroxyethyl)phenol, 4-(3-Hydroxypropyl)-1-sulfonamidobenzene, D,L-2-(Hydroxymethyl)tetrahydrofuran, Methyl lactate, 5-Hydroxyhexanoic acid, methyl ester, 3-Methoxypropanol, 3-Hydroxypiperidine, Pentanol, 4-Hydroxyheptane, 4-(2-Hydroxyethyl)-
- 25 1,2-dimethoxybenzene, 4-Hydroxymethyl-1,2-methylenedioxybenzene, 4-(Trifluoromethyl)benzyl alcohol, 4-(Methylthio)pheno, 2-(Hydroxymethyl)furan, 5-Hydroxypentan-2-one, 2-Hydroxy-3-methylbutanoic acid, methyl ester, 2-Hydroxy-3-phenyl-propanoic acid, ethyl ester, 1-(Hydroxymethyl)naphthalene, 3-Phenylpropanol, 3,3-
- 30 Dimethylbutanol, 3-(2-Hydroxyethyl)fluorobenzene, 4-Hydroxy-1-carboethoxypiperidine, (R)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-Hydroxy-3-methylbutanol, (R)-2-Hydroxy-3-methylbutanol, (S)-2-Hydroxy-propanol, 3,4-Dihydroxytetrahydrofuran, 1,1,1,3,3,3-hexfluoroisopropanol, 2-

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Fluorobenzyl alcohol, tert-Butanol, 2-Hydroxy-1-phenylethanol, iso-Butanol, 4-(2-Hydroxyethyl)fluorobenzene, 3-(Hydroxymethyl)toluene, 2-Chlorobenzyl alcohol, 2,4-Dichlorobenzyl alcohol, sec-Butanol, R-2-Hydroxypropanol, Butanol, 4-Chlorobenzyl alcohol, 2-Ethoxyethanol, 2-  
5 (2-Hydroxyethyl)chlorobenzene, 2-(N-Methyl-N-phenylamino)ethanol, 3-(Trifluoromethyl)benzyl alcohol, 2-(Trifluoromethyl)benzyl alcohol, 2-(Hydroxyethyl)tetrahydrofuran, 4-Phenylbutanol, Nonyl alcohol, 2,6-Difluorobenzyl alcohol, 2-(Hydroxymethyl)thiophene, 2-(Hydroxyethyl)-1-methylpyrrole, 2-Hydroxy-3-methylbutane, 4-Hydroxymethyl-1,2-  
10 dichlorobenzene, 3-(Methylamino)propanol, 1,4-Difluorobenzyl alcohol, (2-Hydroxymethyl)furan,

#### EXAMPLE 29

N-Methyl nodulisporamide and 26-epi-N-methyl nodulisporamide

15 To 1 mg nodulisporic acid in 1 mL dimethylformamide at room temperature was added 2 mg HCl•H<sub>2</sub>NMe, 2 mg N-hydroxybenzotriazole and 10 µL diisopropylethylamine to which was added 2 mg EDC•HCl. After 30 minutes, the reaction was quenched by addition of methanol and  
20 1 drop glacial acetic acid. The solution was diluted with brine, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The reaction was partially purified by preparative TLC (1 x 0.5 mm silica gel plate) using 6:3:1 EtOAc/acetone/methanol. N-Methyl nodulisporamide and 26-epi-N-methyl nodulisporamide were  
25 purified to homogeneity by reversed-phase HPLC using a 60 minute linear gradient from 25:75 to 100:0 acetonitrile/water. The purified products were characterized by <sup>1</sup>H NMR and mass spectrometry.

#### EXAMPLE 30

30 N-(n-Propyl)-nodulisporamide

To 0.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 2 drops diisopropylethylamine, 5 mg H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP.

- 45 -

After 30 minutes at room temperature, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude was partially purified by silica gel flash chromatography using 0.5:5:95  $\text{NH}_4\text{OH}/\text{MeOH}/\text{CHCl}_3$  as  
5 eluant followed by reversed-phase HPLC purification using 20:80 water/methanol as eluant. The product was characterized by  $^1\text{H}$  NMR.

#### EXAMPLE 31

##### 4-Morpholinyl-nodulisporamide

10

To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop morpholine and 2 mg N-hydroxybenzotriazole. 2 mg pyBOP was then added. After 1 hour at room temperature, the solution was filtered  
15 through 2 inches silica gel in a pipet without workup using ethyl acetate as eluant. The resultant solution was concentrated under reduced pressure and pure product was obtained following reversed-phase HPLC using 20:80 water/MeOH as eluant. The product was characterized by  $^1\text{H}$  NMR.

20

#### EXAMPLE 32

##### N-(2-Hydroxyethyl)-nodulisporamide

To 0.5 mg nodulisporic acid in 1 mL methylene chloride at  
25 room temperature was added 2 drops diisopropylethylamine, 5 mg  $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}$ , 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 30 minutes, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC  
30 using 20:80 water/methanol as eluant and the product was characterized by  $^1\text{H}$  NMR and mass spectrometry.

#### EXAMPLE 33

##### N-(1-Methoxycarbonyl-2-hydroxyethyl)-nodulisporamide

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To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 2 drops diisopropylethylamine, 5 mg  $\text{HCl} \cdot \text{H}_2\text{NCH}(\text{CH}_2\text{OH})\text{CO}_2\text{Me}$ , 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 30 minutes, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Pure product was obtained following reversed-phase HPLC using 20:80 water/methanol as eluant and the product was characterized by  $^1\text{H}$  NMR.

10

#### EXAMPLE 34

##### Nodulisporamide and 31-amino-31,32-dihydro-nodulisporamide

To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop  $\text{NH}_4\text{OH}$  and 2 mg N-hydroxybenzotriazole. To this was added 3 mg PyBOP and the solution was stirred for 15 min. The reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. Pure nodulisporamide was obtained following preparative TLC (1 x 0.5 mm silica gel) using 1:9 methanol/chloroform as eluant. Nodulisporamide was characterized by  $^1\text{H}$  NMR and mass spectrometry. Also obtained from this reaction was 31-amino-31,32-dihydro-nodulisporamide.

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#### EXAMPLE 35

##### N-(Methoxycarbonylmethyl)-nodulisporamide

To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 2 mg N-hydroxybenzotriazole and 2 mg  $\text{HCl} \cdot \text{H}_2\text{NCH}_2\text{CO}_2\text{Me}$ . To this solution was added 2 mg PyBOP. After 30 min, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried using  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Pure product was obtained following reversed-phase HPLC purification using

30

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17.5:82.5 water/methanol as eluant. The product was characterized by <sup>1</sup>H NMR and mass spectrometry.

### EXAMPLE 36

#### 5 N,N-Tetramethylene-nodulisporamide

To 125 mg nodulisporic acid in 10 mL methylene chloride at 0°C was added 0.18 mL diisopropylethylamine, 0.15 mL pyrrolidine followed by 108 mg PyBOP. After 5 minutes, the solution was warmed  
10 to room temperature. After 1.5 hours, the solution was poured in 25 mL saturated NaHCO<sub>3</sub>, extracted with methylene chloride, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Pure N,N-tetramethylene-nodulisporamide was obtained following reversed-phase HPLC purification using 50:50 acetonitrile/water as eluant (isocratic for  
15 ten min), followed by a linear 30 minute gradient to 75:25 acetonitrile/water. Pure product (26 mg) was characterized by <sup>1</sup>H NMR and MS.

### EXAMPLE 37

#### 20 N-Ethyl 29,30-dihydro-20,30-oxa-nodulisporamide

To 1 mg Compound B in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop CH<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub>, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 15  
25 minutes, the reaction was quenched with 2 mL saturated NaHCO<sub>3</sub>, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

30

### EXAMPLE 38

#### N-(2-Hydroxyethyl)-29,30-dihydro-20,30-oxa-nodulisporamide

- 48 -

To 0.7 mg Compound B in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop HOCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP.

5 After 15 minutes, the reaction was quenched with 2 mL saturated NaHCO<sub>3</sub>, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using first 20:80 water/methanol then 15:85 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

10

#### EXAMPLE 39

N-(2-Hydroxyethyl)-31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporamide

15 To 1 mg Compound C in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop HOCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 15 minutes, the reaction was quenched with 2 mL saturated NaHCO<sub>3</sub>, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC  
20 using first 20:80 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

#### Example 40

N-tert-Butyl Nodulisporamide

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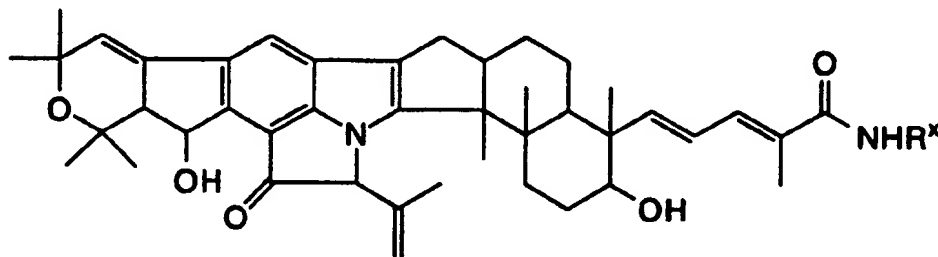
To a solution of 30 mg of nodulisporic acid in 3 mL methylene chloride at 0 °C was added 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. The solution was stirred for 10 minutes and then 0.05 mL tert-butylamine was added. The  
30 solution was stirred overnight at 4 °C and then poured into 1/1 saturated sodium bicarbonate/brine, extracted with methylene chloride and the combined organic layers dried over sodium sulfate. The solids were removed by filtration and the solution concentrated to dryness under reduced pressure. The residue was partially purified by preparative TLC

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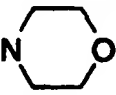

on silica gel (one 1000 micron plate) using 1/2 acetone/hexanes as eluant. Additional purification using HPLC (6/4 acetonitrile/water for 15 minutes, then a 45 minute linear gradient to 7/3 acetonitrile/water) yielded pure product (17 mg). The purified product was characterized by proton  
 5 NMR and MS ( $m/z$ : 735.7 ( $M+1$ )).

The general procedure of Example 40 was repeated using the appropriate amines listed in Table 3 below to provide the corresponding monosubstituted nodulisporamide compounds. These compounds were  
 10 characterized by proton NMR and/or mass spectrometry (unless otherwise specified,  $m/z$  is for  $M+1$ ).

Table 3: Monosubstituted Aliphatic Nodulisporamide Derivatives



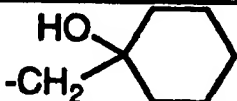
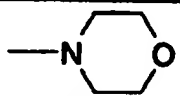

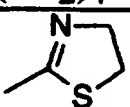
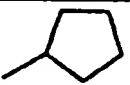
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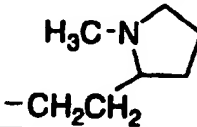
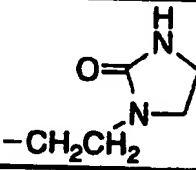
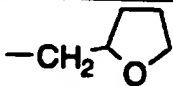
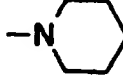
Ex.	$m/z$	Amines	$R^X$
41	796.5	Aminoacetaldehyde diethyl acetal	$CH_2CH(OCH_2CH_3)_2$
42	767.6	(2-Hydroxyethoxy)-ethylamine	$CH_2CH_2OCH_2CH_2OH$
43	792.5	4-(2-Aminoethyl)-morpholine	$-CH_2CH_2-N$ 
44	790.4	1-(2-Aminoethyl)-piperidine	$-CH_2CH_2-N$ 
45	807.5	6-Amino-2-methylheptan-2-ol	$CH(CH_3)(CH_2)_3C(CH_3)_2OH$
46	737.5	3-Aminopropanol	$(CH_2)_3OH$

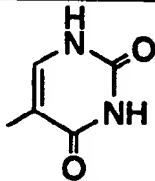
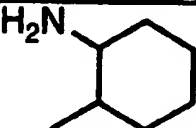
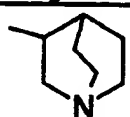
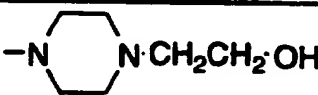
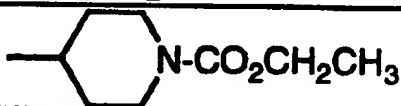
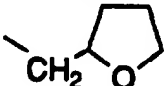
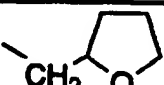
- 50 -

47	751.5	4-Aminobutanol	$(\text{CH}_2)_4\text{OH}$
48	765.6	5-Aminopentanol	$(\text{CH}_2)_5\text{OH}$
49	791.5	1-(2-Aminoethyl)- piperazine	$-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} \text{N}$
50	804.6	1-(3-Aminopropyl)-2- pyrrolidinone	$-(\text{CH}_2)_3-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} \text{C}=\text{O}$
51	776.4	1-(2-Aminoethyl)- pyrrolidine	$-(\text{CH}_2)_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array}$
52	751.4	2-Aminobutanol	$\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_3$
53	750.5	tert-Butylhydrazine	$\text{NHC}(\text{CH}_3)_3$
54	718.3	Aminoacetonitrile	$\text{CH}_2\text{CN}$
55	779.6	6-Aminohexanol	$(\text{CH}_2)_6\text{OH}$
56	806.8	4-(3-Aminopropyl)- morpholine	$-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} \text{O}$
57	737.4	3-Aminopropan-2-ol	$\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$
58	765.4	2-Aminopentanol	$\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_2\text{CH}_3$
59	777.7	1-Amino-1-cyclopentane- methanol	$\text{HOCH}_2-\begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array}$
60		2-(Methylthio)ethylamine	$\text{CH}_2\text{CH}_2\text{SCH}_3$
61	765.4	2-(Ethylthio)ethylamine	$\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_3$
62	736.5	Glycineamide	$\text{CH}_2\text{CONH}_2$
63	748.4	1-Aminopyrrolidine	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array}$
64		2-Amino-2- (hydroxymethyl)propanol	$\text{CH}(\text{CH}_3)(\text{CH}_2\text{OH})_2$
65	777.6	trans-2- Aminocyclohexanol	$\text{HO} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array}$
66	777.6	1-Amino-4-methyl- piperazine	$-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} \text{N}-\text{CH}_3$

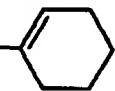
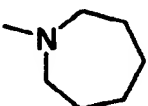


67	766.5	2-(2-Aminoethylamino)-ethanol	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH}$
68	791.4	1-Aminomethyl-cyclohexan-1-ol	
69	779.4	2-Aminohexanol	$\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_3\text{CH}_3$
70	751.5	2-Amino-1-methoxypropane	$\text{CH}(\text{CH}_2\text{OCH}_3)\text{CH}_3$
71	764.4	4-Aminomorpholine	
72	777.6	trans-4-Aminocyclohexan-1-ol	
73	739.4	2-Aminoethanethiol	$(\text{CH}_2)_2\text{SH}$
74	750.5	4-Aminobutylamine	$(\text{CH}_2)_4\text{NH}_2$
75	764.4	2-Amino-4,5-dihydrothiazole	
76	747.5	Aminocyclopentane	
77		2-(Methylsulfonyl)-ethylamine	$\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$
78		2-(Methylsulfinyl)-ethylamine	$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$
79	765.4	2-Amino-3-methylbutanol	$\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$
80	736.5	3-Aminopropylamine	$(\text{CH}_2)_3\text{NH}_2$
81	792.5	3-(Diethylamino)-propylamine	$(\text{CH}_2)_3\text{N}(\text{CH}_2\text{CH}_3)_2$
82	764.5	3-(Dimethylamino)-propylamine	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$
83	723.5	O-Ethylhydroxylamine	$\text{OCH}_2\text{CH}_3$
84	753.5	3-Amino-2-hydroxypropanol	$\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
85	709.4	O-Methylhydroxylamine	$\text{OCH}_3$
86	737.4	2-Methoxyethylamine	$\text{CH}_2\text{CH}_2\text{OCH}_3$

87	764.4	N-Acetylenediamine	$\text{CH}_2\text{CH}_2\text{NHC(O)CH}_3$
88	790.6	2-Aminoethyl-1-methylpyrrolidine	
89	751.5	2-Amino-2-methylpropanol	$\text{C(CH}_3)_2\text{CH}_2\text{OH}$
90	719.4	Cyclopropylamine	$\text{c-C}_3\text{H}_5$
91	760.5	Cyclohexylamine	$\text{c-C}_6\text{H}_{11}$
92	765.5	3-Ethoxypropylamine	$(\text{CH}_2)_3\text{OCH}_2\text{CH}_3$
93	719.5	Allylamine	$\text{CH}_2\text{CH=CH}_2$
94	789.5	2-Amino-2-(hydroxymethyl)butanol	$\text{C(CH}_2\text{CH}_3)(\text{CH}_2\text{OH})_2$
95	717.5	Propargylamine	$\text{CH}_2\text{C}\equiv\text{CH}$
96	765.5	Glycine ethyl ester	$\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$
97	725.7	2-Fluoroethylamine	$\text{CH}_2\text{CH}_2\text{F}$
98	905.5	3-(Dodecyloxy)propylamine	$(\text{CH}_2)_3\text{O(CH}_2)_{11}\text{CH}_3$
99	751.0	2-(Dimethylamino)ethylamine	$\text{CH}_2\text{CH}_2\text{N(CH}_3)_2$
100	791.4	1-(2-Aminoethyl)imidazolone	
101	766.4	2-(2-Aminoethoxy)ethylamine	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$
102		2,2,2-Trifluoroethylamine	$\text{CH}_2\text{CF}_3$
103	780.5	Ethyl hydrazinoacetate	$\text{NHCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$
104	763.5	D,L-2-(Aminomethyl)tetrahydrofuran	
105		1-Aminopiperidine	
106	765.6	D-Alanine methyl ester	$\text{CH(CH}_3)\text{CO}_2\text{CH}_3$

107	777.5	4-Amino-4-methyl-pentan-2-one	$C(CH_3)_2CH_2C(O)CH_3$
108	837.6	Diethyl 2-aminomalonate	$CH(CO_2CH_2CH_3)_2$
109		5-Aminouracil	
110	707.6	Ethylamine	$CH_2CH_3$
111	807.8	Norleucine methyl ester	$CH(CH_2CH_2CH_3)CO_2CH_3$
112	751.7	3-Methoxypropylamine	$CH_2CH_2CH_2OCH_3$
113	745.5	1,1-Dimethylpropargyl-amine	$C(CH_3)_2C\equiv CH$
114	749.7	Pentylamine	$(CH_2)_4CH_3$
115	777.9	4-Aminoheptane	$CH(CH_2CH_2CH_3)_2$
116	763.8	Hexylamine	$(CH_2)_5CH_3$
117	776.8	cis-1,2-Diaminocyclohexane	
118	788.9	3-Aminoquinuclidine	
119	751.7	beta-Alanine	$CH_2CH_2CO_2H$
120	793.5	L-Valine methyl ester	$CH(CH(CH_3)_2)CO_2CH_3$
121		1-Amino-4-(2-Hydroxyethyl)piperazine	
122	753.4	Aminooxyacetic acid	$OCH_2CO_2H$
123	834.5	4-Amino-1-carboethoxypiperidine	
124	763.5	(R)-2-(Aminomethyl)-tetrahydrofuran	
125	763.6	(S)-2-(Aminomethyl)-tetrahydrofuran	

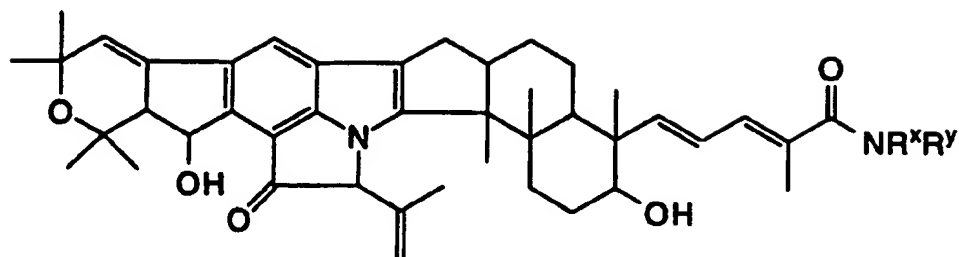
- 54 -

126	765.6	L-Valinol	$\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$
127	765.7	D-Valinol	$\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$
128	737.7	L-Alaninol	$\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$
129	737.6	D-Alaninol	$\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$
130	721.7	Isopropylamine	$\text{CH}(\text{CH}_3)_2$
131	735.7	tert-butylamine	$\text{C}(\text{CH}_3)_3$
132	735.7	iso-Butylamine	$(\text{CH}_2)\text{CH}(\text{CH}_3)_2$
133	735.5	sec-Butylamine	$\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$
134	737.6	(R)-3-Aminopropan-2-ol	$\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$
135	735.6	n-Butylamine	$(\text{CH}_2)_3\text{CH}_3$
136	751.7	2-Ethoxyethylamine	$(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$
137	787.7	2-Aminoethylcyclohexene	$-\text{CH}_2\text{CH}_2-$ 
138	813.7	1-Aminoadamantane	1-adamantyl
139	805.7	n-Nonylamine	$(\text{CH}_2)_8\text{CH}_3$
140	749.8	2-Amino-3-methylbutane	$\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$
141	750.6	3-(Methylamino)-propylamine	$(\text{CH}_2)_3\text{NHCH}_3$
142	778.7	2-(Diethylamino)-ethylamine	$(\text{CH}_2)_2\text{N}(\text{CH}_2\text{CH}_3)_2$
143	776.7	1-Amino-homopiperidine	

The general procedure of Example 40 was repeated using the amines listed in Table 4 below to provide the corresponding nodulisporamide compounds. These compounds were characterized by proton NMR and/or mass spectrometry (unless otherwise specified, m/z is for M+1).

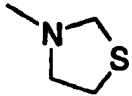
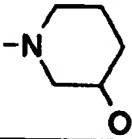
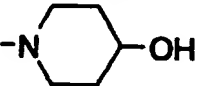

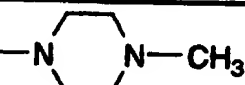
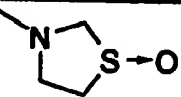
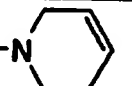
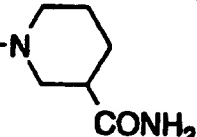
Table 4: Nodulisporamide Derivatives

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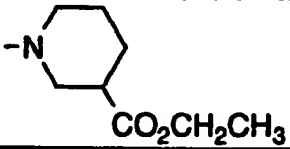
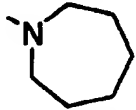
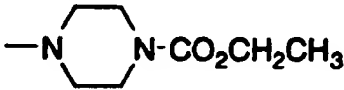

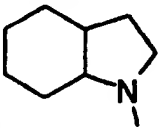
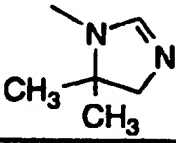
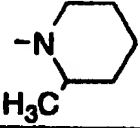
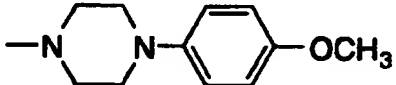


Ex.	m/z	Amine	NR <sup>x</sup> R <sup>y</sup>
144	791.5	1-(2-Aminoethyl)-piperazine	
145	776.6	4-Aminomethylpiperidine	
146	765.4	Thiomorpholine	
147	759.4	Diallylamine	N(CH <sub>2</sub> CH=CH <sub>2</sub> ) <sub>2</sub>
148	737.4	2-(Methylamino)ethanol	N(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> OH
149	795.4	Diisopropanolamine	N(CH <sub>2</sub> CH(CH <sub>3</sub> )OH) <sub>2</sub>
150	763.5	L-2-(Hydroxymethyl)-pyrrolidine	
151	763.5	D-2-(Hydroxymethyl)-pyrrolidine	
152	749.5	3-Hydroxypyrrolidine	
153	732.7	Methylaminoacetonitrile	N(CH <sub>3</sub> )CH <sub>2</sub> C≡N
154		4-(2-hydroxyethyl)-piperazine	
155	777.7	4-Ethylpiperazine	
156	721.5	N-Ethylmethylamine	N(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
157	735.6	N-(Methyl)isopropylamine	N(CH <sub>3</sub> )CH(CH <sub>3</sub> ) <sub>2</sub>

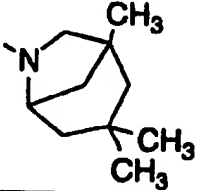
- 56 -

158	735.5	N-Methylpropylamine	$N(CH_3)CH_2CH_2CH_3$
159	749.5	N-Methylbutylamine	$N(CH_3)CH_2CH_2CH_2CH_3$
160	765.7	N-Ethyl-2-methoxyethyl-amine	$N(CH_2CH_3)CH_2CH_2OCH_3$
161	751.7	N-Methyl-2-methoxyethyl-amine	$N(CH_3)CH_2CH_2OCH_3$
162	749.7	N-Ethylpropylamine	$N(CH_2CH_3)CH_2CH_2CH_3$
163	751.5	Tetrahydrothiazole	
164	767.8	Diethanolamine	$N(CH_2CH_2OH)_2$
165	763.8	3-Hydroxypiperidine	
166	763.9	4-Hydroxypiperidine	
167	749.6	N-(Ethyl)isopropylamine	$N(CH_2CH_3)CH(CH_3)_2$
168	747.8	Piperidine	
169	735.8	Diethylamine	$N(CH_2CH_3)_2$
170	762.7	4-Methylpiperazine	
171	767.6	Tetrahydrothiazole-S-oxide	
172	791.7	Dibutylamine	$N(CH_2CH_2CH_2CH_3)_2$
173	745.7	1,2,3,6-Tetrahydropyridine	
174	790.8	3-(Carboxamido)piperidine	

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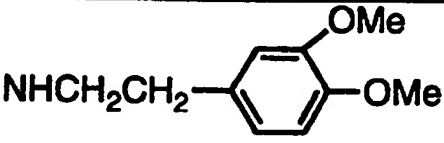
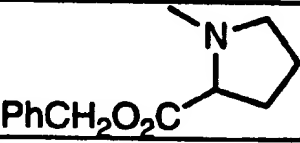
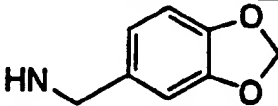
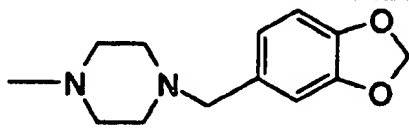
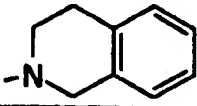
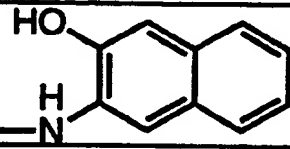
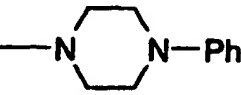
175	819.6	3-(Carboethoxy)piperidine	
176	761.6	Hexamethyleneimine	
177	820.7	1-(Carboethoxy)piperazine	
178	819.7	Dipentylamine	$N(CH_2CH_2CH_2CH_2CH_3)_2$
179	775.6	Heptamethyleneimine	
180	787.6	Octahydroindole	
181	760.5	4,5-Dihydro-5,5-dimethylimidazole	
182	707.5	Dimethylamine	$N(CH_3)_2$
183	763.7	Dipropylamine	$N(CH_2CH_2CH_3)_2$
184	761.7	2-Methylpiperidine	
185	779.5	2-(Butylamino)ethanol	$N((CH_2)_2CH_3)CH_2CH_2OH$
186	731.7	Methylpropargylamine	$N(CH_3)CH_2C\equiv CH$
187	854.7	1-(4-Methoxyphenyl)-piperazine	
188	931.9	Dinonylamine	$N((CH_2)_8CH_3)_2$
189	903.8	Dioctylamine	$N((CH_2)_7CH_3)_2$

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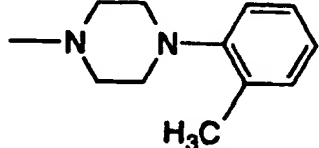
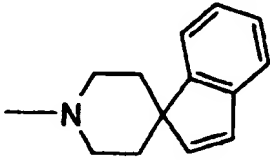
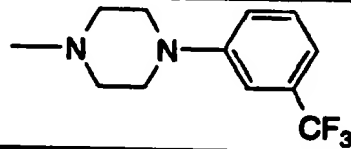
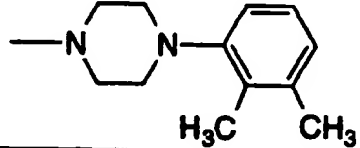
190	815.7	4,6,6-Trimethyl-2-aza[3.2.1]bicyclooctane	
191	750.7	N,N'-Dimethylethylene-diamine	$N(CH_3)(CH_2)_2NHCH_3$
192	750.6	3-(Methylamino)-propylamine	$N(CH_3)(CH_2)_3NH_2$
193	813.7	L-2-Amino-3-phenylpropanol	$NHCH(CH_2OH)CH_2Ph$
194	785.6	2-Amino-4-methylphenol	$NHPh(2-OH,4-CH_3)$
195		4-Aminobenzylamine	$NHCH_2Ph(4-NH_2)$
196	789.4	4-Chloroaniline	$NHPh(4-Cl)$
197	799.5	4-(2-Hydroxyethyl)aniline	$NHPh(4-CH_2CH_2OH)$
198	799.5	2-(2-Hydroxyethyl)aniline	$NHPh(2-CH_2CH_2OH)$
199	783.4	2-Phenylethylamine	$NHCH_2CH_2Ph$
200	785.4	2-(Hydroxymethyl)aniline	$NHPh(2-CH_2OH)$
201	798.8	3-(Dimethylamino)aniline	$NHPh(3-N(CH_3)_2)$
202	835.1	4-(Sulfonylamido)aniline	$NHPh(4-SO_2NH_2)$
203		Phenylhydrazine	$NHNHPh$
204	798.4	2-Carboxamidoaniline	$NHPh(2-CONH_2)$
205	799.8	4-(Aminoethyl)phenol	$NHCH_2CH_2Ph(4-OH)$
206	884.5	4-(3-Aminopropyl)-1-sulfonamidobenzene	$NHCH_2CH_2Ph(4-SO_2NH_2)$
207	770.5	2-Aminoaniline	$NHPh(2-NH_2)$
208	883.7	L-Leucine benzyl ester	$NHCH(CH_2CH(CH_3)_2)CO_2CH_2Ph$
209	888.5	4-(tert-butyl)benzyl-sulfonamide	$NHSO_2CH_2Ph(4-C(CH_3)_3)$
210	833.6	Benzylsulfonamide	$NHSO_2CH_2Ph$
211	788.7	2-Fluorophenylhydrazine	$NHNHPh(2-F)$



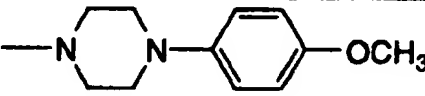
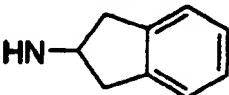
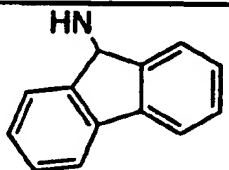
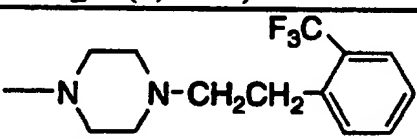
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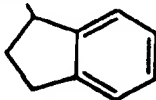
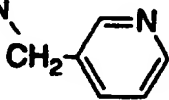
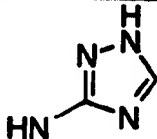
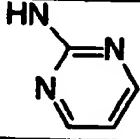
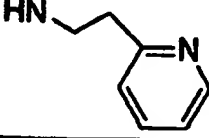
212	843.8	4-(2-Aminoethyl)-1,2-dimethoxybenzene	
213	867.5	L-Proline benzyl ester	
214	813.8	4-Aminomethyl-1,2-methylenedioxybenzene	
215	837.5	4-(Trifluoromethyl)-benzylamine	NHCH2Ph(4-CF3)
216	882.6	1-((3,4-methylenedioxy)-benzyl)piperazine	
217	862.7	3-(Benzyloxy)aniline	NHPh(4-OCH2Ph)
218	801.4	4-(Methylthio)aniline	NHPh(4-SCH3)
219	855.5	L-Phenylalanine ethyl ester	NHCH(CH2Ph)CO2CH2CH3
220	841.4	D-Phenylalanine methyl ester	NHCH(CH2Ph)CO2CH3
221	799.4	4-(Methoxy)benzylamine	NHCH2Ph(4-OCH3)
222	819.5	1-(Aminomethyl)naphthalene	NHCH2-1-naphthyl
223	792.4	1,2,3,4-Tetrahydro-isoquinoline	
224	821.8	3-Amino-2-hydroxy-naphthalene	
225	801.7	3-(2-Aminoethyl)-fluorobenzene	NHCH2CH2(3-F)Ph
226	823.7	4-Phenylpiperazine	
227	814.7	D-Phenylalaninol	NHCH(CH2Ph)CH2OH

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

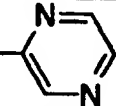
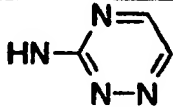
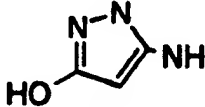
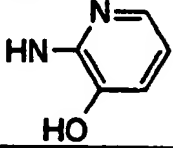
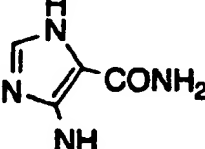

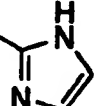
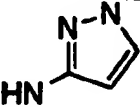
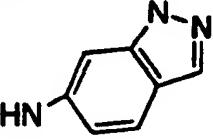
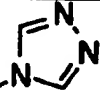
228	838.6	1-(o-Tolyl)piperazine	
229	847.6	Spiro(1H-indene-1,4'-piperidine)	
230	773.6	4-Fluoroaniline	NHPh(4-F)
231	787.5	2-Fluorobenzylamine	NHCH <sub>2</sub> Ph(2-F)
232	799.7	2-Amino-1-phenylethanol	NHCH <sub>2</sub> CH(Ph)OH
234	801.8	4-(2-Aminoethyl)-1-fluorobenzene	NHCH <sub>2</sub> CH <sub>2</sub> Ph(4-F)
235	829.5	4-(2-Amino-2-methylpropyl)-1-fluorobenzene	NHC(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> Ph(3-F)
236	791.7	3,4-Difluoroaniline	NHPh(3,4-diF)
237	783.7	3-(Aminomethyl)toluene	NHCH <sub>2</sub> Ph(3-CH <sub>3</sub> )
238	784.5	3-Methylphenylhydrazine	NHNH(3-CH <sub>3</sub> )Ph
239	803.5	2-Chlorobenzylamine	NHCH <sub>2</sub> Ph(2-Cl)
240	838.8	2,4-Dichlorobenzylamine	NHCH <sub>2</sub> Ph(2,4-diCl)
241	782.7	4-Methylphenylhydrazine	NHNHPh(4-CH <sub>3</sub> )
242	803.8	4-Chlorobenzylamine	NHCH <sub>2</sub> Ph(4-Cl)
243	797.7	3-Phenylpropylamine	NH(CH <sub>2</sub> ) <sub>3</sub> Ph
244	817.6	4-(2-Aminoethyl)-1-chlorobenzene	NHCH <sub>2</sub> CH <sub>2</sub> Ph(4-Cl)
245	893.8	1-(m-Trifluoromethyl phenyl)piperazine	
246	852.6	1-(2,3-Dimethylphenyl)piperazine	

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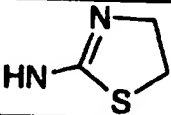
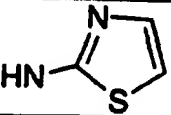
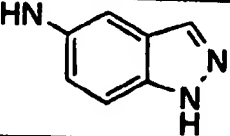
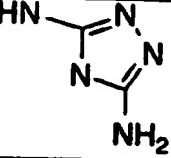
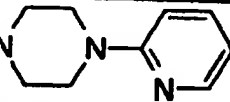
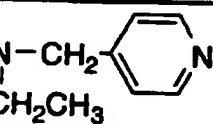
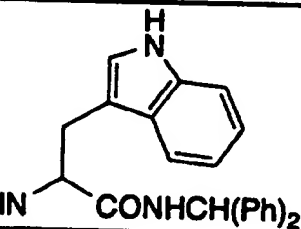
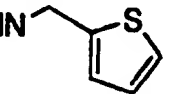
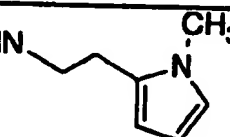
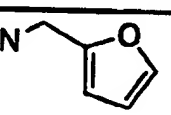
247	812.7	N-Methyl-N-phenyl-ethylenediamine	$\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Ph}$
248	837.6	3-(Trifluoromethyl)-benzylamine	$\text{NHCH}_2\text{Ph}(3\text{-CF}_3)$
249	837.7	2-(Trifluoromethyl)-benzylamine	$\text{NHCH}_2\text{Ph}(2\text{-CF}_3)$
250		1-(4-Methoxyphenyl)-piperazine	
251	795.7	2-Aminoindane	
252	843.6	9-Aminofluorene	
253	811.7	4-Phenylbutylamine	$\text{NH}(\text{CH}_2)_4\text{Ph}$
254	827.8	(R,R)-2-Methylamino-3-phenylbutane	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
255	827.8	(S,S)-2-Methylamino-3-phenylbutane	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
256	825.9	Benzylbutylamine	$\text{N}(\text{CH}_2\text{Ph})(\text{CH}_2)_3\text{CH}_3$
257	785.6	O-Benzylhydroxylamine	$\text{NH}\text{OCH}_2\text{Ph}$
258	805.5	2,6-Difluorobenzylamine	$\text{NCH}_2\text{Ph}(2,6\text{-diF})$
259	920.9	1-(2-(o-Trifluoromethyl-phenyl)ethyl)piperazine	
260	797.7	(S)-N,alpha-Dimethylbenzylamine	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
261	783.7	(S)-alpha-Methylbenzylamine	$\text{NHCH}(\text{CH}_3)\text{Ph}$
262	797.6	Methyl benzyl amine	$\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$
263		4-Aminomethyl-1,2-dichlorobenzene	$\text{NHCH}_2\text{Ph}(3,4\text{-diCl})$

264	783.7	(R)-alpha-Methylbenzylamine	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
265	873.8	1-Benzylamino-2-phenylethane	$\text{N}(\text{CH}_2\text{Ph})\text{CH}_2\text{CH}_2\text{Ph}$
266	784.6	Benzylhydrazine	$\text{NHNHCH}_2\text{Ph}$
267	805.7	2,4-Difluorobenzylamine	$\text{NHCH}_2\text{Ph}(2,4\text{-diF})$
268	838.8	2,5-Dichlorophenylhydrazine	$\text{NHNHPh}(2,5\text{-diCl})$
269	787.7	3-Fluorobenzylamine	$\text{NHCH}_2\text{Ph}(3\text{-F})$
270	795.5	1-Aminoindane	HN 
271	859.8	1,2-Diphenylethylamine	$\text{NHCH}(\text{Ph})\text{CH}_2\text{Ph}$
272	801.8	3,4-Dihydroxybenzylamine	$\text{NHCH}_2\text{Ph}(3,4\text{-diOH})$
273	829.7	2,4-Dimethoxybenzylamine	$\text{NHCH}_2\text{Ph}(3,4\text{-diOCH}_3)$
274	783.8	N-Benzylmethylamine	$\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$
275	797.7	N-Benzylethylamine	$\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Ph}$
276		(R)-N,alpha-Dimethylbenzylamine	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
277	770.5	3-(Aminomethyl)pyridine	HN CH <sub>2</sub> 
278	745.9	3-Amino-1,2,4-triazole	
279	757.4	2-Aminopyrimidine	HN 
280	784.6	2-(2-Aminoethyl)pyridine	HN 

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281	787.5	1-(3-Aminopropyl)-imidazole	HN—(CH <sub>2</sub> ) <sub>3</sub> 
282	770.6	4-(Aminomethyl)pyridine	-NHCH <sub>2</sub> — 
283	757.4	2-Aminopyrazine	HN— 
284		3-Amino-1,2,4-triazine	HN— 
285		5-Amino-3-hydroxypyrazole	
286		2-Amino-3-hydroxypyridine	
287		4-Amino-5-carboxamidoimidazole	
288	770.4	2-(Aminomethyl)pyridine	-NHCH <sub>2</sub> — 
289	751.5 M+Li	2-Aminoimidazole	HN— 
290	745.4	3-Aminopyrazole	HN— 
291	795.2	6-Aminobenzopyrazole	
292	797.5	4-Amino-1,2,4-triazole	HN— 

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293		2-Amino-4,5-dihydrothiazole	
294	762.4	2-Aminothiazole	
295	795.4	5-Aminobenzopyrazole	
296	761.6	3,5-Diamino-1,2,4-triazole	
297	825.7	1-(2-Pyridyl)piperazine	
298	798.7	4-(Ethylaminomethyl)-pyridine	
299	1032.7	L-Tryptophan-1,1-diphenylmethanamide	
300		2-(Aminomethyl)thiophene	
301		2-(2-Aminoethyl)-1-methylpyrrole	
302	759.5	2-(Aminomethyl)furan	

EXAMPLE 303

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### General Procedure for the Preparation of Additional Amide Derivatives of Nodulisporic Acid

To a solution of 30 mg of nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of amine selected from Table 5. Stir the solution overnight at 4 °C and then pour into 1/1 saturated sodium bicarbonate/brine, extract with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution to dryness under reduced pressure. Pure product may be obtained by flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography. The purified product may be characterized by proton NMR and mass spectrometry.

Table 5: Amines for the Preparation of Additional Nodulisporamide Derivatives

N-Methyl-2,2,2-trifluoroethylamine, 2,2,3,3,3-Pentafluoropropylamine, N-Methyl-2,2,3,3,3-pentafluoropropylamine, 1,1,1,3,3,3-Hexafluoroisopropylamine, 2-Difluoro-3-Methoxy-1-methyl-propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine, 1,1,1-Trifluoromethylpropylamine, 2-(3,3,3-Trifluoromethyl)propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine, Di-(2,2,2-trifluoroethyl)amine, N-(2-Methoxyethyl)-2,2,2-trifluoroethylamine, 2-Methoxy-1-methyl-ethylamine, 3-Methoxy-1-methyl-propylamine, 2-Methoxy-1-methyl-ethylamine, N-Methyl-2-methoxy-1-benzyl-ethylamine, 1-Methoxymethyl-3-methyl-butylamine, Methylsulfonamide, Isopropylsulfonamide, Ethylsulfonamide, Benzylsulfonamide, sec-Butylsulfonamide, N-Methyl-ethylsulfonamide, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine, 1-Methyl-propargylamine, 1-Trifluoromethylpropargylamine, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine,

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- N,1,1-Trimethyl-propargylamine, 1-Methyl-propargylamine, 1-Trifluoromethylpropargylamine, N-Ethylpropargylamine, N-(2-Methoxyethyl)propargylamine, 1-Amino-2-pentyne, 1-Amino-3-pentyne, 1-Amino-4-pentyne, 1-Methylamino-2-pentyne, 1-Methylamino-3-pentyne, 1-Methylamino-4-pentyne, 1-Ethylamino-4-pentyne, 1-Trifluoromethylamino-2-pentyne, 1-Trifluoromethylamino-3-pentyne, 1-Trifluoromethylamino-4-pentyne, N-(2-Methoxyethyl)-2-amino-1,1-dimethyl-2-butyne, 1-Amino-2-butyne, 1-Amino-3-butyne, N-Methylamino-2-butyne, N-Methylamino-3-butyne, 1-Ethylamino-3-butyne, 2-(Aminomethyl)dioxane, 2-(2-Aminoethyl)dioxane, 2-(3-Aminopropyl)dioxane, 2-(2-Aminopropyl)dioxane, 2-(Methylaminomethyl)dioxane, 2-(1-Aminoethyl)dioxane, 2-Aminomethyl-2H-tetrahydropyran, 2-(2-Aminoethyl)-2H-tetrahydropyran, 2-(3-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminoethyl)-5-ethyl-2H-tetrahydropyran, 2-Methylaminomethyl-2H-tetrahydropyran, 2-(1-Aminoethyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)tetrahydrofuran, 2-Aminomethyl-5-ethyl-tetrahydrofuran, 2-Methylaminomethyl-tetrahydrofuran, 2-(Ethylaminomethyl)tetrahydrofuran, 2-(1-Aminoethyl)tetrahydrofuran, 4-(Methoxymethyl)benzylamine, 4-(2-Methoxyethyl)benzylamine, 4-(Ethoxymethyl)benzylamine, 4-(Acetoxymethyl)benzylamine, 3-(Dimethylaminomethyl)benzylamine, 4-(Sulfonamidomethyl)benzylamine, 2-Chloro-6-fluoro-benzylamine, 3-Chloro-4-fluoro-benzylamine, 2-Chloro-4-fluoro-benzylamine, 3,5-Difluoro-benzylamine, 2,4-Difluoro-benzylamine, Pentafluorobenzylamine, 4-Methoxy-2,3,5,6-tetrafluorobenzylamine, 4-(Methyl)benzylamine, Benzylamine, 4-(Ethyl)benzylamine, 4-(Ethoxy)benzylamine, 4-(Isopropyl)benzylamine, 4-(Isobutyl)benzylamine, 4-(Isopropoxy)benzylamine, 4-(Isobutoxy)benzylamine, 4-(Allyl)benzylamine, 4-(Allyloxy)benzylamine, 4-(3,3,1,1-Tetrafluoroallyloxy)benzylamine, 4-(Trifluoromethoxy)benzylamine, 4-(2,2,2-trifluoroethoxy)benzylamine, 3,4-Ethylenedioxybenzylamine, 4-Methoxymethyl-2-chloro-



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- phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxyoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-(Methylthio)aniline, 5-(Aminomethyl)benzofuran, 5-(Methylaminomethyl)benzofuran, 4-(1-Aminoethyl)benzofuran, 5-(2-Aminoethyl)benzofuran, 5-Aminomethyl-2,3-dihydro-benzofuran, 5-Methylaminomethyl-2,3-dihydro-benzofuran, 4-1-Aminoethyl-2,3-dihydro-benzofuran, 5-2-Aminoethyl-2,3-dihydro-benzofuran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-1-Aminoethyl-2H-tetrahydrobenzopyran, 5-2-Aminoethyl-2H-tetrahydrobenzopyran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-(1-Aminoethyl)-2H-tetrahydrobenzopyran, 5-(2-Aminoethyl)-2H-tetrahydrobenzopyran, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-1-Aminoethyl-benzo-1,4-dioxane, 5-2-Aminoethyl-benzo-1,4-dioxane, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-(1-Aminoethyl)-benzo-1,4-dioxane, 5-(2-Aminoethyl)-benzo-1,4-dioxane, 3-Amino-5-methoxy-thiophene, 2-Amino-5-chloro-thiophene, 2-(2-Aminoethyl)thiophene, 2-(3-Aminopropyl)thiophene, 3-(3-Aminopropyl)thiophene, 3-(2-Methylaminoethyl)thiophene, 2-Chloro-3-(2-aminoethyl)-thiophene, 2-Aminoethyl-4-methoxy-thiophene, 2-Amino-3-ethyl-thiophene, 2-(Methylaminomethyl)thiophene, 3-(Aminomethyl)thiophene, 2-(2-Aminoethyl)-4-methoxy-thiophene, 1-(Aminomethyl)tetrazole, 1-(1-Aminoethyl)tetrazole, 1-(3-Aminopropyl)tetrazole, 5-Amino-3-methyl-isoxazole, 3-Aminopyridine, 4-Aminomethylthiazole, 2-(2-Aminoethyl)pyrazine, 2-(1-Aminoethyl)imidazole, 2-(Aminomethyl)isoxazole, 3-(2-Aminoethyl)pyrazole, 2-(Aminomethyl)-1,3,4-thiadiazole.

## EXAMPLE 304

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### General Procedure for Synthesis of Amide Derivatives of Compounds B and C

- 5 To a solution of 30 mg of compound B or C in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of an amine selected from Table 6. Stir overnight at 4 °C and then at room temperature for 2 hours. Pour the  
10 solution into 1/1 saturated sodium bicarbonate/brine. Extract the solution with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution under reduced pressure. Pure product may be obtained following purification by flash chromatography, preparative TLC or  
15 reversed-phase liquid chromatography. Products may be characterized by proton NMR and/or mass spectrometry.

TABLE 6: Additional Amide Derivatives of Compounds B and C

- 20 2-(2-Hydroxyethoxy)ethylamine, 4-(2-Aminoethyl)morpholine, 1-(2-Aminoethyl)piperidine, 6-Amino-2-methylheptan-2-ol, 3-(Aminomethyl)pyridine, 3-Aminopropanol, 4-Aminobutanol, 5-Aminopentanol, 2-(2-Aminoethyl)piperidine, 1-(3-Aminopropyl)-2-pyrrolidinone, 1-(2-Aminoethyl)pyrrolidine, 2-Aminobutanol, 4-  
25 (Aminomethyl)pyridine, 2-Aminopyrazine, tert-Butylhydrazine, 6-Aminohexanol, 4-(3-Aminopropyl)morpholine, 3-Aminopropan-2-ol, 2-Aminopentanol, 1-Amino-1-hydroxymethyl-cyclopentane, 2-(Methylthio)ethylamine, 2-(Ethylthio)ethylamine, Thiomorpholine, 4-Amino-5-carboxamidoimidazole, 1-Aminopyrrolidine, 2-Amino-2-  
30 hydroxymethyl-propanol, trans-2-Aminocyclohexan-1-ol, 4-Aminobenzylamine, 2-(Aminomethyl)pyridine, 1-Aminomethyl-cyclohexan-1-ol, 2-Amino-1-methoxypropane, 2-Aminoimidazole, 4-Aminomorpholine, trans-4-Aminocyclohexan-1-ol, 4-Amino-1,2,4-triazole, 2-Amino-4,5-dihydrothiazole, 2-(Methanesulfonyl)ethylamine,

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- 2-(Methanesulfinyl)ethylamine, 4-(2-Hydroxyethyl)aniline, 2-(2-Hydroxyethyl)aniline, 2-Amino-3-methylbutanol, Diallylamine, 2-(Methylamino)ethanol, O-Ethylhydroxylamine, 3-Amino-2-hydroxypropanol, O-Methylhydroxylamine, L-
- 5 (Hydroxymethyl)pyrrolidine, 2-Methoxyethylamine, N-Acetylenediamine, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrrolidine, 2-(Aminoethyl)benzene, 2-Amino-2-methylpropanol, Cyclohexylamine, 3-Ethoxypropylamine, Allylamine, 2-Amino-2-hydroxymethylbutanol, Propargylamine, 2-Fluoroethylamine,
- 10 3-(Dimethylamino)aniline, 2-Dimethylaminoethanol, 4-(2-hydroxyethyl)piperazine, 4-Ethylpiperazine, N-Ethylmethylamine, N-(Methyl)isopropylamine, 2,2,2-Trifluoroethylamine, N-Methylpropylamine, N-Methylbutylamine, N-Ethyl-2-methoxyethylamine, 4-(Aminoethyl)phenol, N-Methyl-2-
- 15 methoxyethylamine, N-Ethylpropylamine, D,L-2-(Aminomethyl)tetrahydrofuran, 1-Aminopiperidine, D-Alanine methyl ester, 3,5-Diamino-1,2,4-triazole, Benzylsulfonamide, 4-Amino-4-methyl-pentan-2-one, 5-Aminouracil, Ethylamine, Norleucine methyl ester, 3-Methoxypropylamine, 3-Hydroxypiperidine, 4-
- 20 Hydroxypiperidine, 1,1-Dimethylpropargylamine, N-(Ethyl)isopropylamine, Pentylamine, Piperidine, 2-Fluorophenylhydrazine, Hexylamine, Diethylamine, 4-(2-Aminoethyl)-1,2-dimethoxybenzene, 1-(2-Pyridyl)piperazine, 4-Methylpiperazine, 4-(2-Hydroxyethyl)morpholine, 4-Aminomethyl-1,2-
- 25 methylenedioxybenzene, 1-((3,4-methylenedioxy)benzyl)piperazine, 4-(Ethylaminomethyl)pyridine, L-Valine methyl ester, D-Phenylalanine methyl ester, 4-(Methoxy)benzylamine, 1-Amino-4-(2-hydroxyethyl)piperazine, 1,2,3,6-Tetrahydropyridine, 3-(2-Aminoethyl)fluorobenzene, 1-Phenylpiperazine, 4-Amino-1-
- 30 carboethoxypiperidine, 1-(Carboethoxy)piperazine, (R)-2-(Aminomethyl)tetrahydrofuran, (S)-2-(Aminomethyl)tetrahydrofuran, L-Valinol, D-Valinol, L-Alaninol, D-Phenylalaninol, 3,4-Dihydroxytetrahydrofuran, D-Alaninol, 2-Fluorobenzylamine, 4-Fluoroaniline, Isopropylamine, tert-Butylamine, iso-Butylamine, 4-(2-

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- Aminoethyl)fluorobenzene, 4,5-Dihydro-5,5-dimethylimidazole, sec-Butylamine, Dimethylamine, (R)-3-Aminopropan-2-ol, Di-n-propylamine, n-Butylamine, 2-Methylpiperidine, 4-Chlorobenzylamine, 3-Phenylpropylamine, 2-Ethoxyethylamine, Methylpropargylamine, 2-
- 5 (Trifluoromethyl)benzylamine, 4-Phenylbutylamine, O-Benzylhydroxylamine, 2,6-Difluorobenzylamine, 2-(Aminomethyl)thiophene, 2-(2-Aminoethyl)-1-methylpyrrole, (S)-N,alpha-Dimethylbenzylamine, 2-Amino-3-methylbutane, (S)-alpha-Methylbenzylamine, 1-Methylamino-2-phenylethane, 3,4-
- 10 Dichlorobenzylamine, 1,4-Difluorobenzylamine, 2-(Aminomethyl)furan, 3-Fluorobenzylamine, 2,4-Dimethoxybenzylamine, N-Benzylmethylamine, N-Ethylbenzylamine, N-Methyl-2,2,2-trifluoroethylamine, 2,2,3,3,3-Pentafluoropropylamine, N-Methyl-2,2,3,3,3-pentafluoropropylamine, 1,1,1,3,3,3-Hexafluoroisopropylamine
- 15 , 2-Difluoro-3-Methoxy-1-methyl-propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine , 1,1,1-Trifluoromethylpropylamine, 2-(3,3,3-Trifluoromethyl)propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine , Di-(2,2,2-trifluoroethyl)amine, N-(2-Methoxyethyl)-2,2,2-trifluoroethylamine, 2-Methoxy-1-methyl-
- 20 ethylamine, 3-Methoxy-1-methyl-propylamine, 2-Methoxy-1-methyl-ethylamine, N-Methyl-2-methoxy-1-benzyl-ethylamine, 1-Methoxymethyl-3-methyl-butylamine, Methylsulfonamide, Isopropylsulfonamide, Ethylsulfonamide, Benzylsulfonamide, sec-Butylsulfonamide, N-Methyl-ethylsulfonamide, N,1,1-Trimethyl-
- 25 propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine, 1-Methyl-propargylamine, 1-Trifluoromethylpropargylamine, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine, N,1,1-Trimethyl-propargylamine, 1-Methyl-propargylamine, 1-
- 30 Trifluoromethylpropargylamine, N-Ethylpropargylamine, N-(2-Methoxyethyl)propargylamine, 1-Amino-2-pentyne, 1-Amino-3-pentyne, 1-Amino-4-pentyne, 1-Methylamino-2-pentyne, 1-Methylamino-3-pentyne, 1-Methylamino-4-pentyne, 1-Ethylamino-4-pentyne, 1-Trifluoromethylamino-2-pentyne, 1-Trifluoromethylamino-3-pentyne, 1-

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- Trifluoromethylamino-4-pentyne, N-(2-Methoxyethyl)-2-amino-1,1-dimethyl-2-butyne, 1-Amino-2-butyne, 1-Amino-3-butyne, N-Methylamino-2-butyne, N-Methylamino-3-butyne, 1-Ethylamino-3-butyne, 2-(Aminomethyl)dioxane, 2-(2-Aminoethyl)dioxane, 2-(3-Aminopropyl)dioxane, 2-(2-Aminopropyl)dioxane, 2-(Methylaminomethyl)dioxane, 2-(1-Aminoethyl)dioxane, 2-Aminomethyl-2H-tetrahydropyran, 2-(2-Aminoethyl)-2H-tetrahydropyran, 2-(3-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminoethyl)-5-ethyl-2H-tetrahydropyran, 2-Methylaminomethyl-2H-tetrahydropyran, 2-(1-Aminoethyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)tetrahydrofuran, 2-Aminomethyl-5-ethyl-tetrahydrofuran, 2-Methylaminomethyl-tetrahydrofuran, 2-(Ethylaminomethyl)tetrahydrofuran, 2-(1-Aminoethyl)tetrahydrofuran, 4-(Methoxymethyl)benzylamine, 4-(2-Methoxyethyl)benzylamine, 4-(Ethoxymethyl)benzylamine, 4-(Acetoxyoxymethyl)benzylamine, 3-(Dimethylaminomethyl)benzylamine, 4-(Sulfonamidomethyl)benzylamine, 2-Chloro-6-fluoro-benzylamine, 3-Chloro-4-fluoro-benzylamine, 2-Chloro-4-fluoro-benzylamine, 3,5-Difluoro-benzylamine, 2,4-Difluoro-benzylamine, Pentafluorobenzylamine, 4-Methoxy-2,3,5,6-tetrafluorobenzylamine, 4-(Methyl)benzylamine, Benzylamine, 4-(Ethyl)benzylamine, 4-(Ethoxy)benzylamine, 4-(Isopropyl)benzylamine, 4-(Isobutyl)benzylamine, 4-(Isopropoxy)benzylamine, 4-(Isobutoxy)benzylamine, 4-(Allyl)benzylamine, 4-(Allyloxy)benzylamine, 4-(3,3,1,1-Tetrafluoroallyloxy)benzylamine, 4-(Trifluoromethoxy)benzylamine, 4-(2,2,2-trifluoroethoxy)benzylamine, 3,4-Ethylenedioxybenzylamine, 4-Methoxymethyl-2-chloro-phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxyoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-

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- (Methylthio)aniline, 5-(Aminomethyl)benzofuran, 5-(Methylaminomethyl)benzofuran, 4-(1-Aminoethyl)benzofuran, 5-(2-Aminoethyl)benzofuran, 5-Aminomethyl-2,3-dihydro-benzofuran, 5-Methylaminomethyl-2,3-dihydro-benzofuran, 4-1-Aminoethyl-2,3-dihydro-benzofuran, 5-2-Aminoethyl-2,3-dihydro-benzofuran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-1-Aminoethyl-2H-tetrahydrobenzopyran, 5-2-Aminoethyl-2H-tetrahydrobenzopyran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-(1-Aminoethyl)-2H-tetrahydrobenzopyran, 5-(2-Aminoethyl)-2H-tetrahydrobenzopyran, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-1-Aminoethyl-benzo-1,4-dioxane, 5-2-Aminoethyl-benzo-1,4-dioxane, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-(1-Aminoethyl)-benzo-1,4-dioxane, 5-(2-Aminoethyl)-benzo-1,4-dioxane, 3-Amino-5-methoxy-thiophene, 2-Amino-5-chloro-thiophene, 2-(2-Aminoethyl)thiophene, 2-(3-Aminopropyl)thiophene, 3-(3-Aminopropyl)thiophene, 3-(2-Methylaminoethyl)thiophene, 2-Chloro-3-(2-aminoethyl)-thiophene, 2-Aminoethyl-4-methoxy-thiophene, 2-Amino-3-ethyl-thiophene, 2-(Methylaminomethyl)thiophene, 3-(Aminomethyl)thiophene, 2-(2-Aminoethyl)-4-methoxy-thiophene, 1-(Aminomethyl)tetrazole, 1-(1-Aminoethyl)tetrazole, 1-(3-Aminopropyl)tetrazole, 5-Amino-3-methyl-isoxazole, 3-Aminopyridine, 4-Aminomethylthiazole, 2-(2-Aminoethyl)pyrazine, 2-(1-Aminoethyl)imidazole, 2-(Aminomethyl)isoxazole, 3-(2-Aminoethyl)pyrazole, 2-(Aminomethyl)-1,3,4-thiadiazole.

## EXAMPLE 305

Methyl 29,30,31,32-tetrahydro-nodulisporate

30

To 1.3 mg methyl nodulisporate in 2 mL 1:1 benzene/water at room temperature was added 1 drop Adogen® 464 (Aldrich Chemical Co., Milwaukee, Wisconsin), 10 mg NaHCO<sub>3</sub> and 10 mg Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>. The solution was heated to 80°C for 10 minutes. The reaction was cooled to

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room temperature, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purified product was obtained following preparative TLC (1 x 0.5 mm silica gel) using 6:4 EtOAc/hexanes as eluant. The purified product was characterized by <sup>1</sup>H NMR.

#### EXAMPLE 306

N-(2-Tetrahydrofuranylmethyl)-29,30,31,32-tetrahydro-nodulisporamide

To 40 mg N-(2-tetrahydrofuranylmethyl)-nodulisporamide in 2 mL methanol at room temperature was added 20 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 2 hours using a balloon. After removal of the catalyst by filtration through Celite using methanol as eluant, the solution was concentrated under reduced pressure and 3 mg pure product was obtained following preparative TLC on silica gel (two 1000 micron plates). The product was characterized by NMR and mass spectrometry (m/z: 767 (M + 1)).

#### EXAMPLE 307

N-Ethyl-N-methyl-29,30,31,32-tetrahydro-nodulisporamide

To 23 mg of N-ethyl-N-methyl-nodulisporamide in 2 mL methanol at room temperature was added 40 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 3 hours using a balloon. After removal of the catalyst by filtration through Celite using methanol as eluant, the solution was concentrated under reduced pressure and 9.5 mg of reduced product was obtained following medium pressure liquid chromatography (93/7 methanol/water as eluant). The product was characterized by proton NMR and mass spectrometry (m/z: 723 (M+1)).

#### EXAMPLE 308

General Procedure for the Preparation of  
29,30,31,32-Tetrahydro-nodulisporic Acid Derivatives

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Place 50 mg of a nodulisporamide or nodulisporate analog prepared from the amines listed in Table 6 or the alcohols listed in Table 2 in 4 mL methanol at room temperature. Hydrogenation may be accomplished using 10% Pd on carbon under 1 atmosphere of hydrogen from 15 minutes to 24 hours. The catalyst may be removed by filtration through a pad of Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired corresponding 29,30,31,32-tetrahydro derivative.

Alternatively, place 50 mg nodulisporic acid in 4 mL methanol at room temperature. Add 1 to 50 mg 10% Pd on carbon and establish an atmosphere of hydrogen using a balloon for 15 minutes to 24 hours. The catalyst may be subsequently removed by filtration through a pad of Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired corresponding 29,30,31,32-tetrahydro-nodulisporic acid. The 29,30,31,32-tetrahydro-nodulisporic acid thus obtained may be coupled to the amines in Table 6 or the alcohols listed in Table 2 to form the desired 29,30,31,32-tetrahydro-amide and ester derivatives.

25

### EXAMPLE 309

#### 29,30-Dihydro-nodulisporic acid

To 1 mg of nodulisporic acid in 1 mL of dichloromethane was added 1.6 mg of Wilkinson's catalyst. The mixture was stirred under a balloon atmosphere of hydrogen overnight (18 h). HPLC separation was obtained with a Magnum 9-ODS reverse phase column and 85:15 methanol:water to 100% methanol gradient. The purified product was isolated upon evaporation of the solvent and characterized by its <sup>1</sup>H NMR.



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**EXAMPLE 311****General Procedure for the Preparation of  
29,30-Dihydro-Nodulisporic Acid Derivatives**

5 To a solution of 30 mg of 29,30-dihydro-nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of an amine or an alcohol selected  
10 from Table 6. Stir overnight at 4 °C and then at room temperature for 2 hours. Pour the solution into 1/1 saturated sodium bicarbonate/brine. Extract the solution with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution under reduced pressure. Pure product may be  
15 obtained following purification by flash chromatography, preparative TLC or reversed-phase liquid chromatography. Products may be characterized by proton NMR and or mass spectrometry.

**EXAMPLE 312****General Procedure for the Preparation of  
31,32-Dihydro-Compound B Derivatives**

20 Place 50 mg of a ester or amide analog prepared from compound B and the amines listed in Table 6 or alcohols listed in Table 2 in 4 mL  
25 methanol at room temperature. Hydrogenation of the 31,32-double bond may be accomplished using 10% Pd on carbon under 1 atmosphere of hydrogen from 15 minutes to 24 hours. The catalyst may be removed by filtration through a pad of Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica  
30 gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired 31,32-dihydro-Compound B derivative.

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Alternatively, place 50 mg compound B in 4 mL methanol at room temperature. Add 1 to 50 mg 10% Pd on carbon and establish an atmosphere of hydrogen using a balloon for 15 minutes to 24 hours. The catalyst may be subsequently removed by filtration through a pad of  
5 Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired corresponding 31,32-dihydro-compound B. The 31,32-dihydro-compound B thus formed may be  
10 coupled to the amines listed in Table 6 and the alcohols listed in Table 2 to form the desired 31,32-dihydro-compound B amides and esters.

#### EXAMPLE 313

##### Nodulisporyl azide

15

To 1 mg of nodulisporic acid in 0.2 mL chloroform was added 50  $\mu$ L triethylamine and 20  $\mu$ L of diphenylphosphoryl azide. The reaction mixture was stirred at room temperature for 3h before purification on silica gel (preparative TLC, 1 x 0.5 mm silica gel) using  
20 1:1 EtOAc/hexanes to yield 0.8 mg of pure product which was characterized by  $^1\text{H}$  NMR and mass spectrometry.

#### EXAMPLE 314

##### 29,30-Dihydro-20,30-oxa-nodulisporyl azide

25

To 1 mg 29,30-dihydro-20,30-oxa-nodulisporic acid in 0.2 mL chloroform add 0.05 mL triethylamine followed by 0.02 mL diphenylphosphoryl azide. Stir the reaction at room temperature for 3 h before purification by flash chromatography or preparative TLC on silica  
30 gel. The product which is obtained may be characterized by proton NMR and mass spectrometry.

#### EXAMPLE 315

##### 29,30-Dihydro-20,30-oxa-32-descarboxy-32-isocyanato-

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**nodulisporic acid**

Heat 20 mg of 29,30-dihydro-20,30-oxa-nodulisporyl azide in 8 mL toluene to 90 °C for 2 h. The solvent may be removed by  
5 evaporation and the product which is obtained may be characterized by proton NMR and mass spectrometry.

**EXAMPLE 316****32-Descarboxy-32-isocyanato-nodulisporic acid**

10

A solution of 54 mg of nodulisporyl azide in toluene was heated at 90°C for 2 h. The solvent was then evaporated and the isocyanate product was obtained in quantitative yield and was characterized by <sup>1</sup>H NMR and mass spectrometry.

15

**EXAMPLE 317****32-Descarboxy-32-(1-carbomethoxyamino)-nodulisporic acid**

To 1.3 mg of isocyanate of Example 313 in 1 mL of  
20 methanol was added 20 microliters of triethylamine. The reaction mixture was heated for 45 min at 75°C and the carbamate product (0.7 mg) was isolated by preparative TLC on silica gel (1 x 0.5 mm) and characterized by <sup>1</sup>H NMR and mass spectrometry.

25

**EXAMPLE 318****32-Descarboxy-32-(1-(3-benzyl)urea)-nodulisporic acid**

To 1 mg of isocyanate of Example 313 in 0.2 mL of toluene was added 40 microliters of benzylamine. The mixture was stirred at  
30 20°C for 20 min and the urea product (0.2 mg) was isolated by preparative TLC (1 x 0.5 mm silica gel, 1:3 hexane:EtOAc) and characterized by its <sup>1</sup>H NMR and MS.

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The general procedure of Example 318 was repeated using the appropriate amine to provide urea compounds of Table 7.

Table 7: 32-Descarboxy-32-[UREA]-Nodulisporic Acid Derivatives

5

Example	Urea
319	NHC(O)-morpholinyl
320	NHC(O)NHCH <sub>2</sub> Ph(4-OMe)
321	NHC(O)NHCH(Me) <sub>2</sub>
322	NHC(O)NH(CH <sub>2</sub> ) <sub>5</sub> NH <sub>2</sub>
323	NHC(O)NHCH <sub>2</sub> CH <sub>2</sub> OH
333	NHC(O)NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>
334	NHC(O)NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -1-morpholinyl
335	NHC(O)NHCH <sub>2</sub> -(2-pyridyl)
336	NHC(O)NHCH <sub>2</sub> CH <sub>2</sub> -piperazinyl

#### EXAMPLE 337

General Procedure for the Synthesis of 32-Descarboxy-32-[UREA]- or 32-Descarboxy-32-[CARBAMATE]-Nodulisporic Acid Derivatives

10

To 1 mg of isocyanate of Example 313 in 0.2 mL of toluene add 40 mg of an amine selected from Table 6 or alcohol selected from Table 2. Stir the mixture at 20°C from 20 minutes to 24 hours. Pure urea or carbamate product may be isolated by flash chromatography, preparative TLC or reversed-phase liquid chromatography. The purified products may be characterized by proton NMR and mass spectrometry.

15

#### EXAMPLE 338

29,30-Dihydro-20,30-oxa-32-descarboxy-32-isocyanato-nodulisporic acid

20

Heat a solution of 54 mg of 29,30-dihydro-20,30-oxa-nodulisporyl azide in toluene at 90°C for 2 h. Evaporate the solvent and

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the isocyanate product thus obtained may be characterized by  $^1\text{H}$  NMR and mass spectrometry.

### EXAMPLE 339

5                   General Procedure for the Synthesis of  
                  29,30-Dihydro-20,30-oxa-32-descarboxy-32-[UREA]- or  
                  29,30-Dihydro-20,30-oxa-32-descarboxy-32-[CARBAMATE]-  
                  Nodulisporic Acid Derivatives

10           To 1 mg of 29,30-dihydro-20,30-oxa-32-descarboxy-32-  
isocyanato-nodulisporic acid in 0.2 mL of toluene add 40 mg of an amine  
selected from Table 6 or alcohol selected from Table 2. Stir the mixture  
at 20°C from 20 minutes to 24 hours. Pure urea or carbamate product  
15           may be isolated by flash chromatography, preparative TLC or reversed-  
phase liquid chromatography. The purified products may be  
characterized by proton NMR and mass spectrometry.

### EXAMPLE 340

20           31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporyl azide

                  To 1 mg 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-  
nodulisporic acid in 0.2 mL chloroform add 0.05 mL triethylamine  
followed by 0.02 mL diphenylphosphoryl azide. Stir the reaction at room  
temperature for 3 h before purification by flash chromatography or  
25           preparative TLC on silica gel. The product which is obtained may be  
characterized by proton NMR and mass spectrometry.

### EXAMPLE 341

30           31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-32-descarboxy-32-  
isocyanato-nodulisporic acid

                  Heat a solution of 54 mg of 31-hydroxy-20,30-oxa-  
29,30,31,32-tetrahydro-nodulisporyl azide in toluene at 90°C for 2 h.

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Evaporate the solvent and the isocyanate product thus obtained may be characterized by  $^1\text{H}$  NMR and mass spectrometry.

#### EXAMPLE 342

5                   General Procedure for the Synthesis of  
31-Hydroxy-20,30-oxa-32-descarboxy-32-[UREA]-29,30,31,32-  
tetrahydro- or 31-Hydroxy-20,30-oxa-32-descarboxy-32-  
[CARBAMATE]-29,30,31,32-tetrahydro-nodulisporic acid Derivatives

10           To 1 mg of 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-32-  
descarboxy-32-isocyanato-nodulisporic acid in 0.2 mL of toluene add 40  
mg of an amine selected from Table 6 or alcohol selected from Table 2.  
Stir the mixture at 20°C from 20 minutes to 24 hours. Pure urea or  
carbamate product may be isolated by flash chromatography, preparative  
15   TLC or reversed-phase liquid chromatography. The purified products  
may be characterized by proton NMR and mass spectrometry.

#### EXAMPLE 343

1-Hydroxy-nodulisporic acid

20           To 2.8 mg of nodulisporic acid in 0.8 mL of THF at 0°C  
under argon was added 100 microliters of 2.0 M lithium borohydride in  
THF. The reaction was quenched with 400 microliters of 2N HCl after 5  
min at 0°C and the products were extracted with EtOAc. The extracts  
25   were dried over sodium sulfate and concentrated in vacuo. The residue  
was purified by preparative TLC (1 x 0.5 mm silica gel plate, 95:5:0.5  
dichloromethane:methanol:acetic acid) to yield 0.8 mg of isomer A and  
0.6 mg of isomer B characterized by their  $^1\text{H}$  NMR and MS.

#### EXAMPLE 344

1-Hydroxy-nodulisporic acid, methyl ester

30           To 0.5 mg methyl nodulisporate in 1 mL methanol at 0°C  
was added 1 mg sodium borohydride. After 10 min at 0°C, the solution

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was purified by reversed-phase HPLC without workup using 30:70 to 15:85 (25 minute linear gradient) water/methanol to yield pure product. The product was characterized by  $^1\text{H}$  NMR.

5

**EXAMPLE 345****N-Ethyl-N-methyl-1-hydroxy-nodulisporamide**

To 30 mg N-ethyl-N-methyl-nodulisporamide in 2 mL tetrahydrofuran at room temperature was added 1 mL  
10 diisobutylaluminum hydride (1.0 M solution in hexanes). After 3 days at room temperature, the reaction was quenched by the addition of acetic acid. The solution was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated to dryness. The residue  
15 was purified by flash chromatography on silica gel using 1/1 acetone/hexanes as eluant. The purified product was characterized by proton NMR and mass spectrometry ( $m/z$ : 723 ( $M+1$ )).

**EXAMPLE 346****1-Hydroxy-Compound B or C**

20

To 5 mg of Compound B or C in 2 mL of methanol at  $0^\circ\text{C}$  under argon add 5 mg of sodium borohydride. After 10 min at  $0^\circ\text{C}$ , extract the products with methylene chloride. Dry the combined extracts over sodium sulfate and concentrate the solution in vacuo. The residual  
25 solid may be purified by flash chromatography, preparative TLC or reversed-phase liquid chromatography to yield 1-hydroxy-Compound B or C as a mixture of stereoisomers which may be characterized by proton NMR and mass spectrometry.

30

**EXAMPLE 347****General Procedure for Synthesis of 1-Hydroxy-Amide and Ester Derivatives of Compounds A, B and C**

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To a solution of 30 mg of 1-hydroxy-Compound A, B or C in 3 mL methylene chloride at 0°C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of an amine selected from Table 6 or an alcohol selected from Table 2. Stir overnight at 4 °C and then at room temperature for 2 hours. Pour the solution into 1/1 saturated sodium bicarbonate/brine. Extract the solution with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution under reduced pressure. Pure product may be obtained following purification by flash chromatography, preparative TLC or reversed-phase liquid chromatography. Products may be characterized by proton NMR and/or mass spectrometry.

**EXAMPLE 348****1-Hydroxy-1-methyl-nodulisporic acid**

To 0.5 mL of 1.4 M methylmagnesium bromide in THF/toluene at 0°C was added 1 mg of nodulisporic acid dissolved in 0.6 mL of THF. After 10 min, the reaction was quenched with 2N HCl and extracted with EtOAc. Preparative TLC (1 x 0.5 mm silica gel plate, 95:5:0.5 dichloromethane:methanol:acetic acid) gave 0.8 mg of product characterized by its <sup>1</sup>H NMR.

**EXAMPLE 349****1-Hydroxy-1-methyl-nodulisporic acid, methyl ester**

To 1.2 mg of methyl nodulisporate in 1 mL of THF under argon at -78°C was added 0.5 mL of 1.4M methylmagnesium bromide in THF/toluene. The mixture was stirred for 15 min before an aqueous solution of ammonium chloride was added. The mixture was extracted with EtOAc. Preparative TLC (1 x 0.5 mm silica gel plate, 2:3 hexane:EtOAc) gave 1 mg of the titled product characterized by its <sup>1</sup>H NMR.



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**EXAMPLE 350****1-Hydroxy-1-Alkyl- or 1-Hydroxy-1-Aryl-Compounds A, B or C**

- To 0.5 mL solution of 1.0 M Grignard reagent selected from Table
- 5 8 in 1/1 THF/toluene at 0°C add 1 mg Compound A, B or C dissolved in 0.6 mL THF. After 10 min at 0°C, quench the reaction with 2N HCl and extract with methylene chloride. Dry the combined organic layers over sodium sulfate, filter and concentrate under reduced pressure. Pure product may be obtained following flash chromatography, preparative
- 10 TLC or reversed-phase liquid chromatography. Purified products may be characterized by proton NMR or mass spectrometry.

**Table 8: Grignard Reagents**

- 15 Methyl magnesium bromide  
Ethyl magnesium chloride  
iso-Propyl magnesium bromide  
Phenyl magnesium iodide  
Benzyl magnesium bromide
- 20 Allyl magnesium bromide  
Propargyl magnesium bromide  
Magnesium bromide acetylde

**EXAMPLE 351**

- 25 1-Hydroxy-32-descarboxy-32-hydroxymethyl-nodulisporic acid

- To 1.2 mg methyl nodulisporate in 1.2 mL tetrahydrofuran at -78°C was added 20 µL 1M lithium aluminum hydride in tetrahydrofuran. The yellow color rapidly disappeared. After 10
- 30 minutes, the reaction was quenched at -78°C by dropwise addition of saturated Na<sub>2</sub>SO<sub>4</sub>. The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Pure product was obtained following preparative TLC (1 x 0.25 mm silica gel

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plate) using 85:15 EtOAc/hexanes as eluant. The purified product was characterized by  $^1\text{H}$  NMR.

#### EXAMPLE 352

5        31,32-Dihydro-31,32-dihydroxy-nodulisporic acid and Aldehyde  
(Compound IV)

To 3 mg of nodulisporic acid was added 1 mL of methanol and 100 microliters of 0.04 M  $\text{OsO}_4$  in t-butanol stabilized with 1% t-butyl hydroperoxide. After 50 min at room temperature, 400 mg of sodium sulfite in 2 mL of water was then added to the reaction mixture and stirring was continued for another 20 minutes. The mixture was then extracted with EtOAc and the crude products were purified by preparative TLC (1 x 0.5 mm silica gel plate) eluted in 95:5:0.5 dichloromethane:methanol:acetic acid to yield the title compound (1 mg isomer A and 0.6 mg isomer B) and 0.5 mg of aldehyde derived from nodulisporic acid (Compound IV), each characterized by  $^1\text{H}$  NMR.

#### EXAMPLE 353

20    General Procedure for the Preparation of Ester and Amide Derivatives of  
31,32-Dihydro-31,32-dihydroxy-nodulisporic acid

To a solution of 30 mg of 31,32-dihydro-31,32-dihydroxy-nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of amine listed in Table 6 or an alcohol listed in Table 2. Stir the solution overnight at 4 °C and then pour into 1/1 saturated sodium bicarbonate/brine, extract with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution to dryness under reduced pressure. Pure product may be obtained by flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography. The purified product may be characterized by proton NMR and mass spectrometry.

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**EXAMPLE 354****4,20-bis-O-Acetyl-nodulisporic acid**

5           To 1.2 mg of nodulisporic acid was added 300 microliters of acetic anhydride and 100 microliters of pyridine. The reaction mixture was heated at 65°C for 1 h and excess solvent was removed in vacuo. The residual solid was purified by preparative TLC on silica gel eluted with 95:5 dichloromethane:methanol to yield 1.2 mg of the bis-acetate  
10       characterized by its <sup>1</sup>H NMR.

**EXAMPLE 355****N-Ethyl-N-methyl-20-dimethylaminocarbonyloxy-nodulisporamide**

15           To 30 mg N-ethyl-N-methyl-nodulisporamide in 3 mL methylene chloride at 4 °C was added 60 mg carbonyldiimidazole. After 3 days at 4 °C, 1 mL dimethylamine (25% in water) was added and the solution stirred for an additional 4 days. The solution was poured into brine, extracted with methylene chloride, dried with sodium sulfate and  
20       evaporated to dryness. Product was partially purified by flash chromatography on silica gel using 4/6 acetone/hexanes as eluant. Additional purification using medium pressure liquid chromatography (92/8 methanol/water as eluant) yielded 18 mg pure product. The purified product was characterized by proton NMR and mass  
25       spectrometry (m/z: 792 (M+1)).

**EXAMPLE 356****N-Ethyl-N-methyl-1-desoxo-1-methoximino-nodulisporamide**

30           To a solution of 30 mg N-ethyl-N-methyl-nodulisporamide and 30 mg methoxylamine hydrochloride in 4 mL ethanol was added 0.1 mL pyridine. The solution was heated to reflux for 2 days, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with brine, dried over sodium

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sulfate and concentrated to dryness. The residue was purified by preparative TLC on silica gel (two 1000 micron plates) using 1/9 methanol/methylene chloride as eluant. The purified products (26 mg), as a mixture of E- and Z-methoximes, were characterized by proton NMR and mass spectrometry ( $m/z$ : 732 ( $M+1 - 1H_2O$ )).

#### EXAMPLE 357

##### N-Ethyl-N-methyl-1-desoxo-1-oximino-nodulisporamide

To a solution of 20 mg N-ethyl-N-methyl-nodulisporamide and 20 mg hydroxylamine hydrochloride in 2 mL ethanol at room temperature was added 0.02 mL pyridine. The solution was heated to reflux for 15 hours, cooled to room temperature and diluted with methylene chloride. The solution was washed with brine, dried over sodium sulfate and concentrated to dryness. The residue was purified by preparative TLC on silica gel (two 1000 micron plates) using 1/9 methanol/methylene chloride as eluant to yield 17 mg desired product as a mixture of E- and Z-oxime isomers. The purified products were characterized by proton NMR and mass spectrometry ( $m/z$ : 718 ( $M+1 - 1H_2O$ )).

#### EXAMPLE 358

##### General Procedure for the Preparation of 1-Oximino Derivatives of Compounds A, B and C

To a solution of 20 mg of compound A, B or C and 20 mg hydroxylamine derivative selected from Table 9 in 2 mL ethanol at room temperature, add 0.02 mL pyridine. Heat the solution to reflux for 15 minutes to 24 hours, then cool to room temperature and dilute with methylene chloride. The solution may be washed with brine, the organic layer dried over sodium sulfate and concentrated to under reduced pressure. Pure product may be obtained following purification by flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography as a mixture of E- and Z-oxime isomers. The purified products may be characterized by proton NMR and mass spectrometry.

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Similarly, amide and ester derivatives of compounds A, B and C, prepared using the amines listed in Table 6 and alcohols in Table 2, may be substituted for compounds A, B and C in the above procedure.

5    Table 9: Oxime Reagents

- Hydroxylamine
- O-Methylhydroxylamine
- O-Ethylhydroxylamine
- 10    O-Benzylhydroxylamine
- O-tert-Butylhydroxylamine
- O-(Pentafluorobenzyl)hydroxylamine
- O-Allylhydroxylamine
- O-Phenylhydroxylamine
- 15    O-iso-Butylhydroxylamine
- O-(2-Chloro-6-fluoro-benzyl)hydroxylamine
- O-(4-Methoxybenzyl)hydroxylamine

EXAMPLE 359

20        General Procedure for the Preparation of Hydrazinyl Derivatives of  
              Compounds A, B and C

- To a solution of 20 mg of compound A, B or C and 20 mg hydrazine selected from Table 10 in 2 mL ethanol at room temperature,
- 25    add 0.02 mL pyridine. Heat the solution to reflux for 15 minutes to 24 hours, then cool to room temperature and dilute with methylene chloride. The solution may be washed with brine, the organic layer dried over sodium sulfate and concentrated to under reduced pressure. Pure product may be obtained following purification by flash chromatography or
- 30    preparative TLC on silica gel or reversed-phase liquid chromatography as a mixture of E- and Z-oxime isomers. The purified products may be characterized by proton NMR and mass spectrometry. Similarly, amide and ester derivatives of compounds A, B and C, prepared using the

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amines listed in Table 6 and alcohols in Table 2, may be substituted for compounds A, B and C in the above procedure.

**Table 10: Hydrazine Reagents**

5	Methylhydrazine
	N,N-Dimethylhydrazine
	tert-Butylhydrazine
	4-Amino-morpholine
10	1-Amino-pyrrolidine
	1-Amino-piperidine
	Phenylhydrazine
	4-(Methyl)phenylhydrazine
	Benzylhydrazine
15	Ethyl hydrazinoacetate
	2-(Fluoro)phenylhydrazine
	1-Amino-4-methyl-piperazine
	1-Amino-4-(2-hydroxyethyl)piperazine
	2,5-Dichlorophenylhydrazine
20	Methanesulfonyl hydrazide
	iso-Propylsulfonyl hydrazide
	Benzenesulfonyl hydrazide

**EXAMPLE 360**

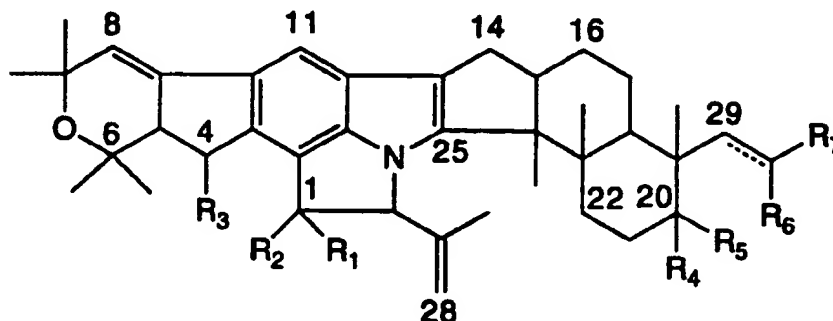
**25 N-Ethyl-N-methyl-26-epi-nodulisporamide**

To a solution of 5 mg N-ethyl-N-methyl-nodulisporamide in 2 mL acetonitrile was added 1 mL triethylamine. The solution was heated to reflux for 20 hours. The solution was concentrated to dryness under  
30 reduced pressure. The residue was purified by flash chromatography on silica gel using 1/9 methanol/methylene chloride to yield the desired product, which was characterized by proton NMR.

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WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

wherein

R<sub>1</sub> is

- (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- (3) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkenyl,
- (4) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkynyl,
- (5) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- (6) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl

where the substituents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from

- (i) C<sub>1</sub>-C<sub>5</sub> alkyl,
- (ii) X-C<sub>1</sub>-C<sub>10</sub> alkyl, where X is O or S(O)<sub>m</sub>.
- (iii) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- (iv) hydroxy,
- (v) halogen,
- (vi) cyano,
- (vii) carboxy,
- (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl,
- (ix) C<sub>1</sub>-C<sub>10</sub> alkanoylamino, and

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- (x) aroyl amino wherein said aroyl is optionally substituted with 1 to 3 groups independently selected from  $R^f$
- 5 (7) aryl C<sub>0</sub>-C<sub>5</sub> alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from  $R^f$ ,
- (8) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl
- 10 (9) a 5- or 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen atoms optionally substituted by 1 to 3 groups independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>10</sub> alkyl and halogen, and which may be saturated or partly unsaturated,
- R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are independently OR<sup>a</sup>, OCO<sub>2</sub>R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>; or
- 15 R<sub>1</sub>+R<sub>2</sub> represent =O, =NOR<sup>a</sup> or =N-NR<sup>c</sup>R<sup>d</sup>;
- R<sub>5</sub> and R<sub>6</sub> are hydrogen; or
- R<sub>5</sub> and R<sub>6</sub> together represent -O-;
- R<sub>7</sub> is (1) CHO, or
- (2) the fragment
- 
- 20 R<sub>8</sub> is (1) hydrogen,
- (2) OR<sup>a</sup>, or
- (3) NR<sup>c</sup>R<sup>d</sup>
- R<sub>9</sub> is (1) hydrogen, or
- (2) OR<sup>a</sup>;
- 25 R<sub>10</sub> is (1) CN,
- (2) C(O)OR<sup>b</sup>,
- (3) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,
- (4) C(O)NR<sup>c</sup>R<sup>d</sup>,
- (5) NHC(O)OR<sup>b</sup>,
- (6) NHC(O)NR<sup>c</sup>R<sup>d</sup>,
- 30 (7) CH<sub>2</sub>OR<sup>a</sup>,



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- (8)  $\text{CH}_2\text{OCO}_2\text{R}^b$ ,
- (9)  $\text{CH}_2\text{OC}(\text{O})\text{NR}^c\text{R}^d$ ,
- (10)  $\text{C}(\text{O})\text{NR}^c\text{NR}^c\text{R}^d$ , or
- (11)  $\text{C}(\text{O})\text{NR}^c\text{SO}_2\text{R}^b$ ;

5      $\text{---}$  represents a single or a double bond;

$\text{R}^a$  is

- (1) hydrogen,
  - (2) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
  - (3) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkenyl,
  - (4) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkynyl,
  - (5) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkanoyl,
  - (6) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkenoyl,
  - (7) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkynoyl,
  - (8) optionally substituted aroyl,
  - (9) optionally substituted aryl,
  - (10) optionally substituted C<sub>3</sub>-C<sub>7</sub> cycloalkanoyl,
  - (11) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkenoyl,
  - (12) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkylsulfonyl
  - (13) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl
  - (14) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl
- where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  $\text{NR}^g\text{R}^h$ ,  $\text{CO}_2\text{R}^b$ ,  $\text{CONR}^c\text{R}^d$  and halogen,
- (15) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl,
  - (16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl, nitro, halogen and cyano,
  - (17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkenyl, C<sub>1</sub>-C<sub>5</sub>

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- R<sup>b</sup> is**
- perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and halogen, and which may be saturated or partly unsaturated;
- (1) hydrogen,
  - (2) optionally substituted aryl,
  - (3) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
  - (4) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkenyl,
  - (5) optionally substituted C<sub>3</sub>-C<sub>10</sub> alkynyl,
  - (6) optionally substituted C<sub>3</sub>-C<sub>15</sub> cycloalkyl,
  - (7) optionally substituted C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, or
  - (8) optionally substituted 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen; where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from
    - (i) hydroxy,
    - (ii) C<sub>1</sub>-C<sub>6</sub> alkyl,
    - (iii) oxo,
    - (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,
    - (v) aryl C<sub>1</sub>-C<sub>6</sub> alkoxy,
    - (vi) hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl,
    - (vii) C<sub>1</sub>-C<sub>12</sub> alkoxy,
    - (viii) hydroxy C<sub>1</sub>-C<sub>6</sub> alkoxy,
    - (ix) amino C<sub>1</sub>-C<sub>6</sub> alkoxy,
    - (x) cyano,
    - (xi) mercapto,
    - (xii) C<sub>1</sub>-C<sub>6</sub> alkyl-S(O)<sub>m</sub>,
    - (xiii) C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with 1 to 4 groups independently selected from R<sup>e</sup>,
    - (xiv) C<sub>5</sub>-C<sub>7</sub> cycloalkenyl,
    - (xv) halogen,
    - (xvi) C<sub>1</sub>-C<sub>5</sub> alkanoyloxy,
    - (xvii) C(O)NR<sup>g</sup>R<sup>h</sup>,
    - (xviii) CO<sub>2</sub>R<sup>i</sup>,

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- (xix) formyl,
- (xx)  $-NR^gR^h$ ,
- (xxi) 5 to 9-membered heterocycle, which may  
 5 be saturated or partially unsaturated, containing from 1 to 4  
 heteroatoms independently selected from oxygen, sulfur and  
 nitrogen, and optionally substituted with 1 to 5 groups  
 independently selected from  $R^e$ ,
- (xxii) optionally substituted aryl, wherein the  
 10 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 independently selected from  $R^e$ ,
- (xxiii) optionally substituted aryl  $C_1$ - $C_3$  alkoxy,  
 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from  $R^e$ , and
- (xxiv)  $C_1$ - $C_5$  perfluoroalkyl;
- 15  $R^c$  and  $R^d$  are independently selected from  $R^b$ ; or  
 $R^c$  and  $R^d$  together with the N to which they are attached form a 3- to 10-  
 membered ring containing 0 to 2 additional heteroatoms  
 selected from O,  $S(O)_m$ , and N, optionally substituted with 1  
 to 3 groups independently selected from  $R^g$ , hydroxy, thioxy  
 20 and oxo;
- $R^e$  is
- (1) halogen,
- (2)  $C_1$ - $C_7$  alkyl,
- (3)  $C_1$ - $C_3$  perfluoroalkyl,
- (4)  $-S(O)_mR^i$ ,
- 25 (5) cyano,
- (6) nitro,
- (7)  $R^iO(CH_2)_v-$ ,
- (8)  $R^iCO_2(CH_2)_v-$ ,
- (9)  $R^iOCO(CH_2)_v$ ,
- 30 (10) optionally substituted aryl where the substituents  
 are from 1 to 3 of halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, or  
 hydroxy,
- (11)  $SO_2NR^gR^h$ , or
- (12) amino;

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- R<sup>f</sup>** is
- (1) C<sub>1</sub>-C<sub>4</sub> alkyl,
  - (2) X-C<sub>1</sub>-C<sub>4</sub> alkyl, where X is O or S(O)<sub>m</sub>,
  - (3) C<sub>2</sub>-C<sub>4</sub> alkenyl,
  - (4) C<sub>2</sub>-C<sub>4</sub> alkynyl,
  - 5 (5) C<sub>1</sub>-C<sub>3</sub>-perfluoroalkyl,
  - (6) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl,
  - (7) hydroxy,
  - (8) halogen, and
  - 10 (9) C<sub>1</sub>-C<sub>5</sub> alkanoyl amino,
- R<sup>g</sup>** and **R<sup>h</sup>** are independently
- (1) hydrogen,
  - (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>
  - 15 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;
  - 20 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
  - (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,
  - (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (10) aminocarbonyl,
  - 25 (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl
  - (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or
- R<sup>g</sup>** and **R<sup>h</sup>** together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- 30 **R<sup>i</sup>** is
- (1) hydrogen,
  - (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (3) C<sub>1</sub>-C<sub>6</sub> alkyl,

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(4) optionally substituted aryl C<sub>0</sub>-C<sub>6</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy;

5    m is        0 to 2; and  
      v is        0 to 3; or  
      a pharmaceutically acceptable salt thereof; and  
      excluding nodulisporic acid, 29,30-dihydro-20,30-oxa-nodulisporic acid,  
      and 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-  
 10    nodulisporic acid.

2.        A compound of Claim 1

wherein  
 R<sub>1</sub> is

15    (1)        hydrogen,  
      (2)        optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
      (3)        optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl,  
      (4)        optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl,  
      (5)        optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
      (6)        optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl  
 20    where the substituents on the alkyl, alkenyl, alkynyl,  
      cycloalkyl and cycloalkenyl are 1 to 3 groups independently  
      selected from

25    (i)        C<sub>1</sub>-C<sub>3</sub> alkyl,  
      (ii)       X-C<sub>1</sub>-C<sub>6</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
      (iii)      C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
      (iv)      hydroxy,  
      (v)        halogen,  
      (vi)       cyano,  
      (vii)      carboxy, and  
 30    (viii)     NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are  
      independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,  
      (7)        aryl C<sub>0</sub>-C<sub>3</sub> alkyl wherein said aryl is optionally  
      substituted with 1 to 3 groups independently selected from  
      R<sup>f</sup>,

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- (8) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (9) a 5- or 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen atoms optionally substituted by 1 to 3 groups independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl and halogen, and which may be saturated or partly unsaturated,
- 5 R<sub>8</sub> is (1) hydrogen,
- (2) OH, or
- (3) NH<sub>2</sub>;
- 10 R<sub>9</sub> is (1) hydrogen or
- (2) OH;
- R<sub>10</sub> is (1) C(O)OR<sup>b</sup>,
- (2) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,
- (3) C(O)NR<sup>c</sup>R<sup>d</sup>,
- 15 (4) NHC(O)OR<sup>b</sup>,
- (5) NHC(O)NR<sup>c</sup>R<sup>d</sup>,
- (6) CH<sub>2</sub>OR<sup>a</sup>,
- (7) CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup>,
- (8) CH<sub>2</sub>OC(O)NR<sup>c</sup>R<sup>d</sup>,
- 20 (9) C(O)NR<sup>c</sup>NR<sup>c</sup>R<sup>d</sup>, or
- (10) C(O)NR<sup>c</sup>SO<sub>2</sub>R<sup>b</sup>;
- R<sup>a</sup> is (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- (3) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,
- 25 (4) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,
- (5) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkanoyl,
- (6) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenoyl,
- (7) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynoyl,
- (8) optionally substituted aroyl,
- 30 (9) optionally substituted aryl,
- (10) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkanoyl,
- (11) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenoyl,
- (12) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl
- (13) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl

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- 5 (14) optionally substituted C5-C6 cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl,  
 cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl  
 are from 1 to 10 groups independently selected from  
 hydroxy, C1-C4 alkoxy, C5-C6 cycloalkyl, aryl C1-C3  
 alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,
- 10 (15) C1-C3 perfluoroalkyl,  
 (16) arylsulfonyl optionally substituted with 1 to 3  
 groups independently selected from C1-C3 alkyl, C1-C3  
 perfluoroalkyl, halogen and cyano,
- 15 (17) a 5- or 6-membered heterocycle containing 1 to 4  
 heteroatoms selected from oxygen, sulfur and nitrogen  
 optionally substituted by 1 to 4 groups independently  
 selected from C1-C3 alkyl, C1-C3 alkenyl, C1-C3  
 perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and  
 halogen, and which may be saturated or partly unsaturated;
- R<sup>b</sup> is
- 20 (1) hydrogen,  
 (2) optionally substituted aryl,  
 (3) optionally substituted C1-C7 alkyl,  
 (4) optionally substituted C3-C7 alkenyl,  
 (5) optionally substituted C3-C7 alkynyl,  
 (6) optionally substituted C5-C7 cycloalkyl,  
 (7) optionally substituted C5-C7 cycloalkenyl, or
- 25 (8) optionally substituted 5- to 10-membered  
 heterocycle containing from 1 to 4 heteroatoms  
 independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
 cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 30 independently selected from
- (i) hydroxy,  
 (ii) C1-C3 alkyl,  
 (iii) oxo,  
 (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,

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- 5 (v) aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 (vi) hydroxy C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (vii) C<sub>1</sub>-C<sub>7</sub> alkoxy,  
 (viii) hydroxy C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 (ix) amino C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 (x) cyano,  
 (xi) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (xii) C<sub>1</sub>-C<sub>3</sub> alkyl-S(O)<sub>m</sub>,  
 10 (xiii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted  
 with 1 to 4 groups independently selected from R<sup>e</sup>,  
 (xiv) C<sub>5</sub>-C<sub>6</sub> cycloalkenyl,  
 (xv) halogen,  
 (xvi) C<sub>1</sub>-C<sub>3</sub> alkanoyloxy,  
 (xvii) C(O)NR<sup>g</sup>R<sup>h</sup>,  
 15 (xviii) CO<sub>2</sub>R<sup>i</sup>,  
 (xix) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from R<sup>e</sup>,  
 (xx) -NR<sup>g</sup>R<sup>h</sup>,  
 20 (xxi) 5- to 6-membered heterocycle, which  
 may be saturated or partially unsaturated, containing from 1  
 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen, and optionally substituted with 1 to 5 groups  
 independently selected from R<sup>e</sup>, and  
 25 (xxii) optionally substituted aryl, wherein the  
 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 independently selected from R<sup>e</sup>;
- Re is
- 30 (1) halogen,  
 (2) C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (4) -S(O)<sub>m</sub>R<sup>i</sup>,  
 (5) cyano,  
 (6) amino,  
 (7) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,



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- (8)  $R^iCO_2(CH_2)_v-$ ,  
 (9)  $R^iOCO(CH_2)_v$ ,  
 (10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or hydroxy, or  
 (11)  $SO_2NR^gR^h$ ;  
 R<sup>f</sup> is  
 (1) methyl,  
 (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 (3) halogen,  
 (4) acetylamino,  
 (5) trifluoromethyl,  
 (6)  $NY^1Y^2$ , where Y<sup>1</sup> and Y<sup>2</sup> are independently H or methyl, and  
 (7) hydroxy;  
 R<sup>g</sup> and R<sup>h</sup> are independently  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>  
 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;  
 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,  
 (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (10) aminocarbonyl,  
 (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl  
 (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or  
 R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;

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- R<sup>i</sup> is**  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (3) C<sub>1</sub>-C<sub>4</sub> alkyl,  
 (4) optionally substituted aryl C<sub>0</sub>-C<sub>4</sub> alkyl, where the  
 5 aryl substituents are from 1 to 3 groups independently  
 selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and  
 hydroxy;  
 all other variables are as defined in Claim 1.
- 10 **3. A compound of Claim 1**  
 wherein  
**R<sub>1</sub> is**  
 (1) hydrogen,  
 (2) optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (3) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkenyl,  
 15 (4) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkynyl,  
 where the substituents on the alkyl, alkenyl, and alkynyl are  
 1 to 3 groups independently selected from  
 (i) methyl,  
 (ii) X-methyl, where X is O or S(O)<sub>m</sub> and  
 20 (iii) halogen,  
 (5) aryl C<sub>0</sub>-C<sub>1</sub> alkyl wherein said aryl is optionally  
 substituted with 1 to 3 groups independently selected from  
 R<sup>f</sup>,  
 (6) trifluoromethyl
- 25 **R<sub>8</sub> is**  
 (1) hydrogen,  
 (2) OH, or  
 (3) NH<sub>2</sub>
- R<sub>9</sub> is**  
 (1) hydrogen, or  
 (2) OH;
- 30 **R<sub>10</sub> is**  
 (1) C(O)OR<sup>b</sup>,  
 (2) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,  
 (3) C(O)NR<sup>c</sup>R<sup>d</sup>,  
 (4) NHC(O)OR<sup>b</sup>,  
 (5) NHC(O)NR<sup>c</sup>R<sup>d</sup>,

- (6)  $\text{CH}_2\text{OR}^a$ ,  
 (7)  $\text{CH}_2\text{OCO}_2\text{R}^b$ ,  
 (8)  $\text{CH}_2\text{OC}(\text{O})\text{NR}^c\text{R}^d$ ,  
 (9)  $\text{C}(\text{O})\text{NR}^c\text{NR}^c\text{R}^d$ , or  
 (10)  $\text{C}(\text{O})\text{NR}^c\text{SO}_2\text{R}^b$ ;  
 5  $\text{R}^a$  is  
 (1) hydrogen,  
 (2) optionally substituted  $\text{C}_1$ - $\text{C}_4$  alkyl,  
 (3) optionally substituted  $\text{C}_3$ - $\text{C}_4$  alkenyl,  
 (4) optionally substituted  $\text{C}_3$ - $\text{C}_4$  alkynyl,  
 10 (5) optionally substituted  $\text{C}_1$ - $\text{C}_4$  alkanoyl,  
 (6) optionally substituted aroyl,  
 (7) optionally substituted  $\text{C}_5$ - $\text{C}_6$  cycloalkanoyl,  
 (8) optionally substituted  $\text{C}_5$ - $\text{C}_6$  cycloalkenoyl,  
 (9) optionally substituted  $\text{C}_1$ - $\text{C}_3$  alkylsulfonyl  
 15 where the substituents on the alkyl, alkenyl, alkynyl,  
 alkanoyl, aroyl, cycloalkanoyl, cycloalkenoyl, and  
 alkylsulfonyl, are from 1 to 5 groups independently selected  
 from hydroxy,  $\text{C}_1$ - $\text{C}_2$  alkoxy, aryl  $\text{C}_1$ - $\text{C}_3$  alkoxy,  $\text{NR}^g\text{R}^h$ ,  
 $\text{CO}_2\text{R}^b$ ,  $\text{CONR}^c\text{R}^d$  and halogen,  
 20 (10) trifluoromethyl,  
 (11) arylsulfonyl optionally substituted with 1 to 3  
 groups independently selected from methyl, trifluoromethyl  
 and halogen,  
 (12) a 5- or 6-membered heterocycle containing 1 to 4  
 25 heteroatoms selected from oxygen, sulfur and nitrogen  
 optionally substituted by 1 to 4 groups independently  
 selected from methyl, trifluoromethyl,  $\text{C}(\text{O})\text{NR}^c\text{R}^d$ ,  $\text{CO}_2\text{R}^b$   
 and halogen, and which may be saturated or partly  
 unsaturated;  
 30  $\text{R}^b$  is  
 (1) hydrogen,  
 (2) optionally substituted aryl,  
 (3) optionally substituted  $\text{C}_1$ - $\text{C}_6$  alkyl,  
 (4) optionally substituted  $\text{C}_3$ - $\text{C}_6$  alkenyl,  
 (5) optionally substituted  $\text{C}_3$ - $\text{C}_6$  alkynyl,

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- (6) optionally substituted C5-C6 cycloalkyl,  
 (7) optionally substituted C5-C6 cycloalkenyl, or  
 (8) optionally substituted 5- to 6-membered  
 heterocycle containing from 1 to 4 heteroatoms  
 independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
 cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 independently selected from
- (i) hydroxy,
  - (ii) C1-C3 alkyl,
  - (iii) oxo,
  - (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,
  - (v) aryl C1-C3 alkoxy,
  - (vi) hydroxy C1-C4 alkyl,
  - (vii) C1-C4 alkoxy,
  - (viii) hydroxy C1-C4 alkoxy,
  - (ix) amino C1-C4 alkoxy,
  - (x) cyano,
  - (xi) C1-C4 alkyl-S(O)<sub>m</sub>,
  - (xii) C5-C6 cycloalkyl optionally substituted  
 with 1 to 4 groups independently selected from R<sup>e</sup>,
  - (xiii) C5-C6 cycloalkenyl,
  - (xiv) halogen,
  - (xv) C1-C3 alkanoyloxy,
  - (xvi) C(O)NR<sup>g</sup>R<sup>h</sup>,
  - (xvii) CO<sub>2</sub>R<sup>i</sup>,
  - (xviii) -NR<sup>g</sup>R<sup>h</sup>,
  - (xix) 5- to 6-membered heterocycle, which  
 may be saturated or partially unsaturated, containing from 1  
 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen, and optionally substituted with 1 to 5 groups  
 independently selected from R<sup>e</sup>,

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(xx) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R<sup>e</sup>,

5 (xxi) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R<sup>e</sup>, and

(xxii) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl;

R<sup>e</sup> is

- (1) halogen,
- (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
- 10 (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (4) -S(O)<sub>m</sub>R<sup>i</sup>,
- (5) cyano,
- (6) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
- (7) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
- 15 (8) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,
- (9) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or hydroxy,

(10) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>, or

20

(11) amino;

R<sup>f</sup> is

- (1) methyl,
- (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,
- (3) trifluoromethyl,
- (4) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or
- 25 methyl,
- (5) hydroxy,
- (6) halogen, and
- (7) acetylamino,

R<sup>g</sup> and R<sup>h</sup> are independently

30

- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>

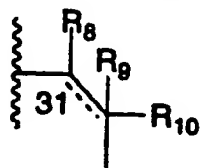
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- (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C1-C7 alkoxy, C1-C7 alkyl or C1-C3 perfluoroalkyl,
- (4) aryl C1-C6 alkyl, wherein the aryl is optionally substituted with C1-C3 perfluoroalkyl or 1,2-methylenedioxy;
- (5) C1-C5 alkoxy carbonyl,
- (6) C1-C5 alkanoyl,
- (7) C1-C5 alkanoyl C1-C6 alkyl,
- (9) aryl C1-C5 alkoxy carbonyl,
- (10) aminocarbonyl,
- (11) C1-C5 monoalkylaminocarbonyl
- (12) C1-C5 dialkylaminocarbonyl; or
- R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- R<sup>i</sup> is
- (1) hydrogen,
- (2) C1-C3 perfluoroalkyl,
- (3) C1-C4 alkyl,
- (4) optionally substituted aryl C0-C6 alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C1-C6 alkyl, C1-C6 alkoxy, and hydroxy
- all other variables are as defined in Claim 1.

25

4. A compound of Claim 1 wherein R<sup>7</sup> is CHO.

5. A compound of Claim 1 wherein R<sup>7</sup> is the fragment



30

R<sup>10</sup> is (1) C(O)OR<sup>b</sup>,

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- (2)  $C(O)N(OR^b)R^c$ ,
- (3)  $C(O)NR^cR^d$ ,
- (4)  $C(O)NR^cNR^cR^d$ , or
- (5)  $C(O)NR^cSO_2R^b$

5  $R^8, R^9, R^b, R^c$  and  $R^d$  are as defined in Claim 1.

6. A compound of Claim 5 wherein  
 $R^{10}$  is  $C(O)OR^b$ ;  
 $R^b$  is

- 10 (1) optionally substituted aryl,
- (2) optionally substituted  $C_1$ - $C_6$  alkyl,
- (3) optionally substituted  $C_3$ - $C_6$  alkenyl,
- (4) optionally substituted  $C_3$ - $C_6$  alkynyl,
- (5) optionally substituted  $C_3$ - $C_6$  cycloalkyl, or
- 15 (6) optionally substituted 5 to 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from
- 20 (i) hydroxy,
- (ii)  $C_1$ - $C_3$  alkyl,
- (iii) oxo,
- (iv)  $SO_2NR^gR^h$ ,
- (v) aryl  $C_1$ - $C_3$  alkoxy,
- 25 (vi) hydroxy  $C_1$ - $C_4$  alkyl,
- (vii)  $C_1$ - $C_4$  alkoxy,
- (viii) hydroxy  $C_1$ - $C_4$  alkoxy,
- (ix) amino  $C_1$ - $C_4$  alkoxy,
- (x) cyano,
- 30 (xi)  $C_1$ - $C_4$  alkyl- $S(O)_m$ ,
- (xii)  $C_5$ - $C_6$  cycloalkyl optionally substituted with 1 to 4 groups independently selected from  $R^e$ ,
- (xiii)  $C_5$ - $C_6$  cycloalkenyl,
- (xiv) halogen,

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- (xv) C<sub>1</sub>-C<sub>3</sub> alkanoyloxy,  
 (xvi) C(O)NR<sup>g</sup>R<sup>h</sup>,  
 (xvii) CO<sub>2</sub>R<sup>i</sup>,  
 (xvii) -NR<sup>g</sup>R<sup>h</sup>,  
 5 (xix) 5 to 6-membered heterocycle, which may be saturated or partially unsaturated, containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 5 groups independently selected from R<sup>e</sup>,  
 10 (xx) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R<sup>e</sup>,  
 (xxi) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 4 groups independently selected from R<sup>e</sup>, and  
 15 (xxii) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl;  
 R<sup>e</sup> is  
 (1) halogen,  
 (2) C<sub>1</sub>-C<sub>7</sub> alkyl,  
 (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl  
 20 (4) nitro,  
 (6) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>,  
 (7) R<sup>i</sup>OC(O)(CH<sub>2</sub>)<sub>v</sub>  
 (8) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,  
 v is 0;  
 25 R<sup>g</sup> and R<sup>h</sup> are independently  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy or CO<sub>2</sub>R<sup>b</sup>,  
 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 30 (4) C<sub>1</sub>-C<sub>5</sub> alkanoyl, or  
 R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms



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- selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- R<sup>i</sup> is (1) hydrogen, or  
(2) C<sub>1</sub>-C<sub>6</sub> alkyl;
- 5 m is 0 to 2; and  
all other variables are as defined in Claim 5.
7. A compound of Claim 5 wherein
- 10 R<sup>10</sup> is (1) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,  
(2) C(O)NR<sup>c</sup>R<sup>d</sup>  
(3) C(O)NR<sup>c</sup>NR<sup>c</sup>R<sup>d</sup>, or  
(4) C(O)NR<sup>c</sup>SO<sub>2</sub>R<sup>i</sup>;
- R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup> and R<sup>i</sup> are as defined in Claim 5.
- 15 8. A compound of Claim 3 wherein
- R<sup>10</sup> is C(O)NR<sup>c</sup>R<sup>d</sup>; and  
R<sup>c</sup> and R<sup>d</sup> are as defined in Claim 3.
9. A compound of Claim 5 wherein
- 20 R<sup>10</sup> is C(O)NR<sup>c</sup>R<sup>d</sup>;
- R<sup>b</sup> is (1) hydrogen,  
(2) optionally substituted aryl,  
(3) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
(4) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,  
25 (5) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,  
(6) optionally substituted C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
(7) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, or  
(8) optionally substituted 5 to 6-membered heterocycle  
containing from 1 to 4 heteroatoms independently selected  
30 from oxygen, sulfur and nitrogen;  
where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
independently selected from  
(i) hydroxy,

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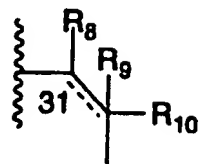
- 5 (ii) C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (iii) oxo,  
 (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,  
 (v) arylC<sub>1</sub>-C<sub>3</sub> alkyl,  
 (vi) hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl,  
 (vii) C<sub>1</sub>-C<sub>12</sub> alkoxy,  
 (viii) hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 (ix) amino C<sub>1</sub>-C<sub>4</sub> alkoxy,  
 10 (x) cyano,  
 (xi) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (xii) C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>m</sub>,  
 (xiii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted  
 with 1 to 4 groups selected from R<sup>e</sup>,  
 (xiv) C<sub>5</sub>-C<sub>6</sub> cycloalkenyl,  
 15 (xv) halogen,  
 (xvi) C(O)NR<sup>g</sup>R<sup>h</sup>,  
 (xvii) CO<sub>2</sub>R<sup>i</sup>,  
 (xviii) -NR<sup>g</sup>R<sup>h</sup>,  
 (xix) 5 to 9-membered heterocycle containing  
 20 from 1 to 4 heteroatoms independently selected from  
 oxygen, sulfur and nitrogen, and optionally substituted with  
 1 to 3 groups independently selected from R<sup>e</sup>,  
 (xx) optionally substituted aryl, wherein the  
 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 25 independently selected from R<sup>e</sup> and  
 (xxi) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from R<sup>e</sup>;  
 R<sup>c</sup> and R<sup>d</sup> are independently selected from R<sup>b</sup>; or  
 30 R<sup>c</sup> and R<sup>d</sup> together with the N to which they are attached form a 3- to 10-  
 membered ring containing 0 to 2 additional heteratoms  
 selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1  
 to 3 groups independently selected from R<sup>g</sup>, hydroxy, thioxy  
 and oxo;

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- R<sup>e</sup>** is
- (1) halogen,
  - (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
  - 5 (5) R<sup>j</sup>iCO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
  - (6) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,
  - (7) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>;
  - (8) amino
- v** is 0;
- 10 **R<sup>g</sup>** and **R<sup>h</sup>** are independently
- (1) hydrogen,
  - (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy ,
  - 15 (3) aryl optionally substituted with halogen, 1,2-  
methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub>  
perfluoroalkyl,
  - (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally  
substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-  
methylenedioxy,
  - 20 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
  - (7) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (8) aminocarbonyl, or
- R<sup>g</sup>** and **R<sup>h</sup>** together with the N to which they are attached form a 5- to 6-
- 25 membered ring containing 0 to 2 additional heteroatoms  
selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1  
to 3 groups independently selected from R<sup>e</sup> and oxo;
- R<sup>i</sup>** is
- (1) hydrogen or
  - 30 (2) optionally substituted C<sub>0</sub>-C<sub>6</sub> alkyl wherein the  
substituents are aryl or substituted aryl, and the aryl  
substituents are from 1 to 3 groups independently selected  
from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy; and  
all other variables are as defined in Claim 5.

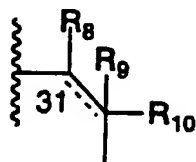
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10. A compound of Claim 1 wherein R<sub>7</sub> is the fragment



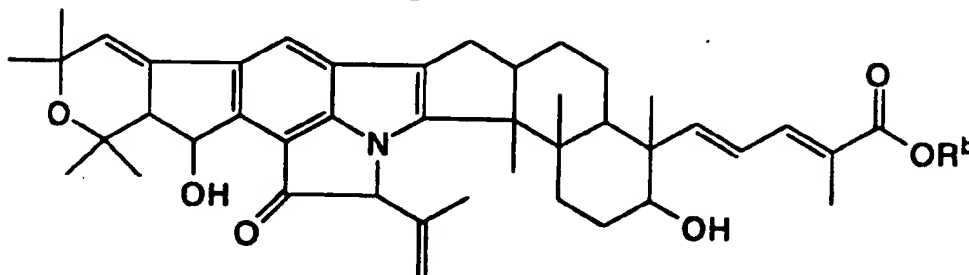
- R<sub>10</sub> is CH<sub>2</sub>OR<sup>a</sup>, NHC(O)OR<sup>b</sup> or NHC(O)NR<sup>c</sup>R<sup>d</sup>;  
 5 R<sub>8</sub>, R<sub>9</sub>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup> and ---- are as defined in Claim 1.

11. A compound of Claim 1 wherein R<sub>7</sub> is the fragment



- 10 R<sub>10</sub> is CO<sub>2</sub>H; and  
 R<sub>8</sub>, R<sub>9</sub> and ---- are as defined in Claim 1.

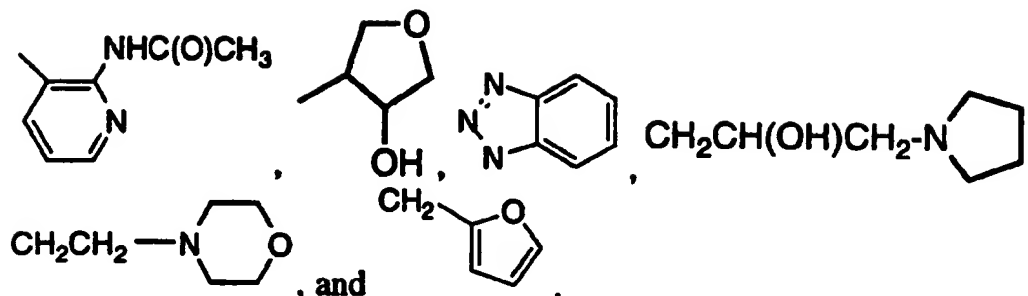
12. A compound of the formula



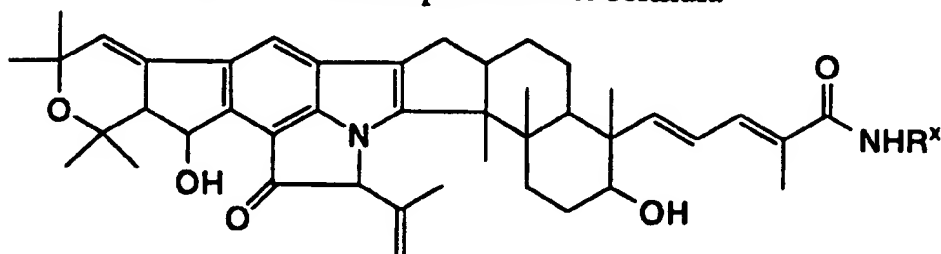
- 15 wherein R<sup>b</sup> is selected from the group consisting of:

- CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>CH<sub>2</sub>N(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>,  
 CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH,  
 CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH(OH)CH<sub>2</sub>N(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>,  
 20 CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>Ph(4-NO<sub>2</sub>), CH<sub>2</sub>Ph(3-NO<sub>2</sub>), CH<sub>2</sub>CF<sub>3</sub>,  
 CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph, CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>,  
 CH(CF<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>Ph(2-CF<sub>3</sub>),

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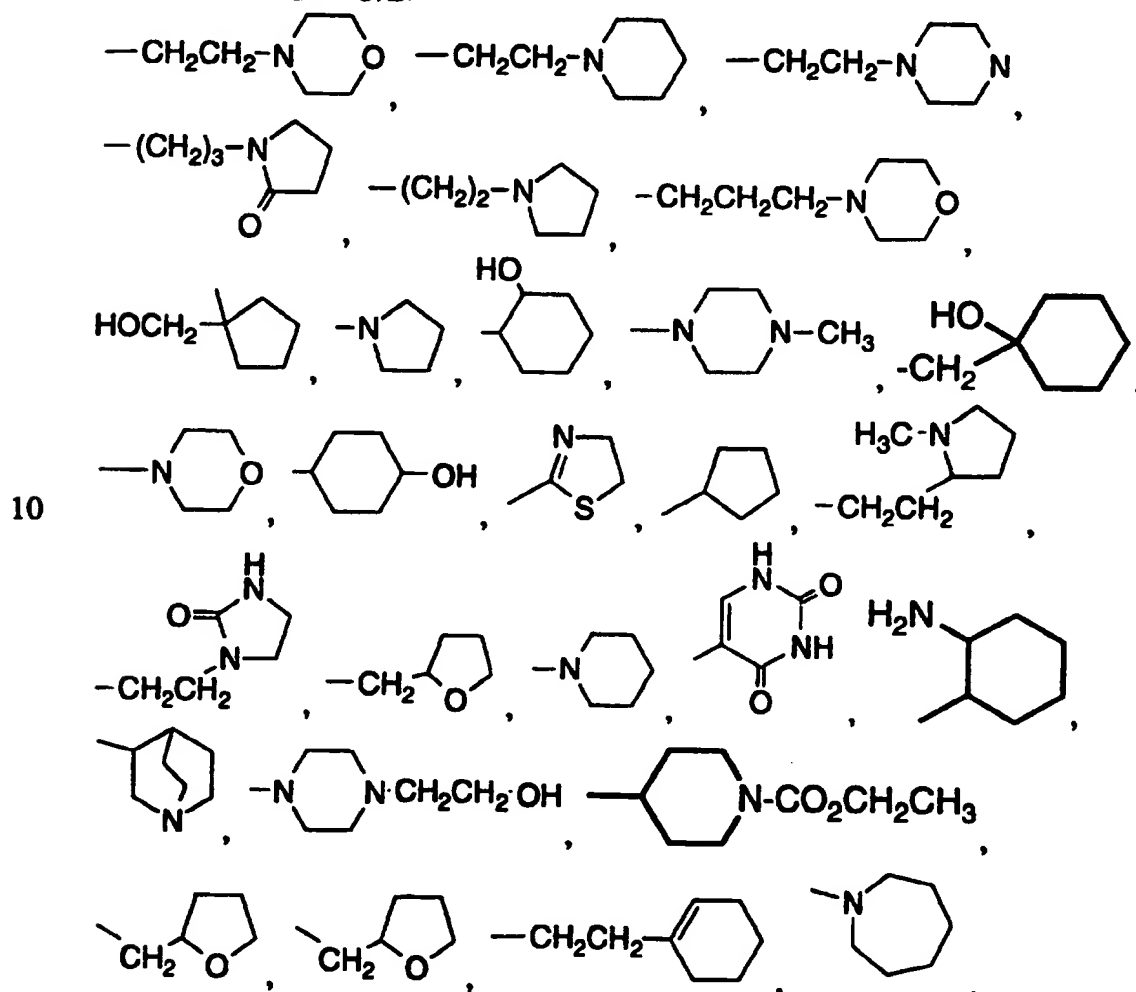


13. A compound of the formula



- 5 wherein  $\text{R}^X$  is selected from the group consisting of:
- H,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_3$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{OH}$ ,  
 $\text{CH}(\text{CO}_2\text{CH}_3)\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)_2$ ,  
 $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ ,  $\text{CH}(\text{CH}_3)(\text{CH}_2)_3\text{C}(\text{CH}_3)_2\text{OH}$ ,  $(\text{CH}_2)_3\text{OH}$ ,  
 10  $(\text{CH}_2)_4\text{OH}$ ,  $(\text{CH}_2)_5\text{OH}$ ,  $\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_3$ ,  $\text{NHC}(\text{CH}_3)_3$ ,  $\text{CH}_2\text{CN}$ ,  
 $(\text{CH}_2)_6\text{OH}$ ,  $\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{SCH}_3$ ,  $\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CONH}_2$ ,  
 $\text{CH}(\text{CH}_3)(\text{CH}_2\text{OH})_2$ ,  $\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH}$ ,  
 $\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_3\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{OCH}_3)\text{CH}_3$ ,  $(\text{CH}_2)_2\text{SH}$ ,  
 15  $(\text{CH}_2)_4\text{NH}_2$ ,  $\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$ ,  
 $\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$ ,  $(\text{CH}_2)_3\text{NH}_2$ ,  $(\text{CH}_2)_3\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  
 $(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$ ,  $\text{OCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$ ,  $\text{OCH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{CH}_2\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$ , *c*- $\text{C}_3\text{H}_5$ , *c*- $\text{C}_6\text{H}_{11}$ ,  $(\text{CH}_2)_3\text{OCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}=\text{CH}_2$ ,  $\text{C}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{OH})_2$ ,  
 20  $\text{CH}_2\text{C}\equiv\text{CH}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{F}$ ,  $(\text{CH}_2)_3\text{O}(\text{CH}_2)_{11}\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$ ,  $\text{CH}_2\text{CF}_3$ ,  
 $\text{NHCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)\text{CO}_2\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$ ,  
 $\text{CH}(\text{CO}_2\text{CH}_2\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CO}_2\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{C}\equiv\text{CH}$ ,  $(\text{CH}_2)_4\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,

(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H, CH(CH(CH<sub>3</sub>)<sub>2</sub>)CO<sub>2</sub>CH<sub>3</sub>, OCH<sub>2</sub>CO<sub>2</sub>H,  
CH(CH(CH<sub>3</sub>)<sub>2</sub>)CH<sub>2</sub>OH, CH(CH(CH<sub>3</sub>)<sub>2</sub>)CH<sub>2</sub>OH, CH(CH<sub>3</sub>)CH<sub>2</sub>OH,  
CH(CH<sub>3</sub>)CH<sub>2</sub>OH, CH(CH<sub>3</sub>)<sub>2</sub>, C(CH<sub>3</sub>)<sub>3</sub>, (CH<sub>2</sub>)CH(CH<sub>3</sub>)<sub>2</sub>,  
CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH(CH<sub>3</sub>)OH, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>,  
5 1-adamantyl, (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>NHCH<sub>3</sub>,  
(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>,

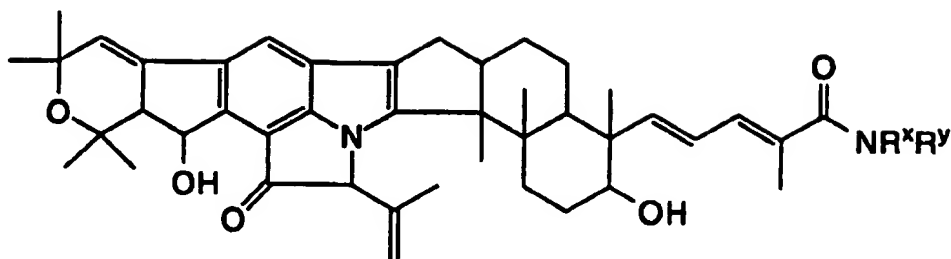


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**14. A compound of the formula**

**A compound of the formula**

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wherein  $\text{NR}^X\text{R}^Y$  is selected from the group consisting of:

- $\text{N}(\text{CH}_3)\text{CH}_2\text{C}\equiv\text{N}$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$ ,  
 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 5  $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  
 $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_2\text{CH}=\text{CH}_2)_2$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  
 $\text{N}(\text{CH}_2\text{CH}(\text{CH}_3)\text{OH})_2$ ,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$ ,  
 $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  
 $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  
 10  $\text{N}((\text{CH}_2)_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{C}\equiv\text{CH}$ ,  $\text{N}((\text{CH}_2)_8\text{CH}_3)_2$ ,  
 $\text{N}((\text{CH}_2)_7\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{NHCH}_3$ ,  $\text{N}(\text{CH}_3)(\text{CH}_2)_3\text{NH}_2$ ,  
 $\text{NHCH}(\text{CH}_2\text{OH})\text{CH}_2\text{Ph}$ ,  $\text{NHPh}(2\text{-OH}, 4\text{-CH}_3)$ ,  $\text{NHCH}_2\text{Ph}(4\text{-NH}_2)$ ,  
 $\text{NHPh}(4\text{-Cl})$ ,  $\text{NHPh}(4\text{-CH}_2\text{CH}_2\text{OH})$ ,  $\text{NHPh}(2\text{-CH}_2\text{CH}_2\text{OH})$ ,  
 $\text{NHCH}_2\text{CH}_2\text{Ph}$ ,  $\text{NHPh}(2\text{-CH}_2\text{OH})$ ,  $\text{NHPh}(3\text{-N}(\text{CH}_3)_2)$ ,  $\text{NHPh}(4\text{-SO}_2\text{NH}_2)$ ,  
 15  $\text{NHNHPh}$ ,  $\text{NHPh}(2\text{-CONH}_2)$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-OH})$ ,  
 $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-SO}_2\text{NH}_2)$ ,  $\text{NHPh}(2\text{-NH}_2)$ ,  
 $\text{NHCH}(\text{CH}_2\text{CH}(\text{CH}_3)_2)\text{CO}_2\text{CH}_2\text{Ph}$ ,  $\text{NH}\text{SO}_2\text{CH}_2\text{Ph}(4\text{-C}(\text{CH}_3)_3)$ ,  
 $\text{NH}\text{SO}_2\text{CH}_2\text{Ph}$ ,  $\text{NHNHPh}(2\text{-F})$ ,  $\text{NHCH}_2\text{Ph}(4\text{-CF}_3)$ ,  $\text{NHPh}(4\text{-OCH}_2\text{Ph})$ ,  
 $\text{NHPh}(4\text{-SCH}_3)$ ,  $\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_2\text{CH}_3$ ,  
 20  $\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_3$ ,  $\text{NHCH}_2\text{Ph}(4\text{-OCH}_3)$ ,  $\text{NHCH}_2\text{-1-naphthyl}$ ,  
 $\text{NHPh}(4\text{-F})$ ,  $\text{NHCH}_2\text{Ph}(2\text{-F})$ ,  $\text{NHCH}_2\text{CH}(\text{Ph})\text{OH}$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-F})$ ,  
 $\text{NHC}(\text{CH}_3)_2\text{CH}_2\text{Ph}(3\text{-F})$ ,  $\text{NHPh}(3,4\text{-diF})$ ,  $\text{NHCH}_2\text{Ph}(3\text{-CH}_3)$ ,  $\text{NHNH}(3\text{-CH}_3)\text{Ph}$ ,  
 $\text{NHCH}_2\text{Ph}(2\text{-Cl})$ ,  $\text{NHCH}_2\text{Ph}(2,4\text{-diCl})$ ,  $\text{NHNHPh}(4\text{-CH}_3)$ ,  
 $\text{NHCH}_2\text{Ph}(4\text{-Cl})$ ,  $\text{NH}(\text{CH}_2)_3\text{Ph}$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-Cl})$ ,  
 25  $\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Ph}$ ,  $\text{NHCH}_2\text{Ph}(3\text{-CF}_3)$ ,  $\text{NHCH}_2\text{Ph}(2\text{-CF}_3)$ ,  
 $\text{NH}(\text{CH}_2)_4\text{Ph}$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  
 $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  $\text{N}(\text{CH}_2\text{Ph})(\text{CH}_2)_3\text{CH}_3$ ,  $\text{NH}\text{OCH}_2\text{Ph}$ ,  
 $\text{NCH}_2\text{Ph}(2,6\text{-diF})$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  $\text{NHCH}(\text{CH}_3)\text{Ph}$ ,  
 $\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$ ,  $\text{NHCH}_2\text{Ph}(3,4\text{-diCl})$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,

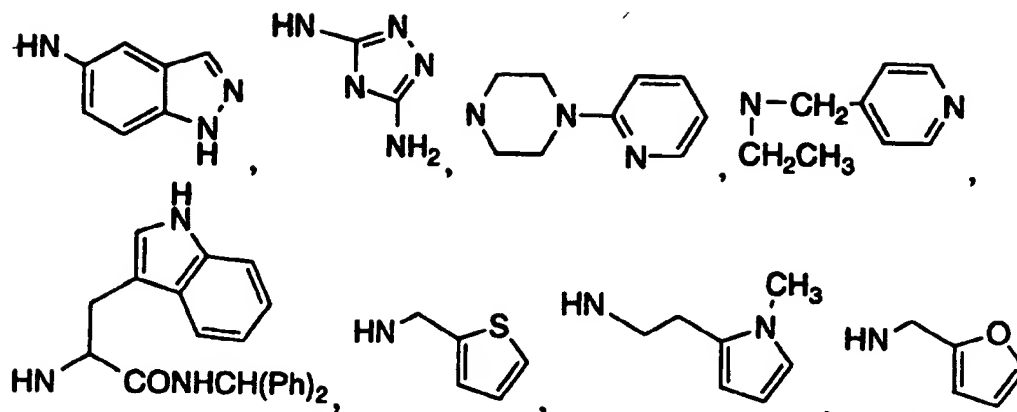
N(CH<sub>2</sub>Ph)CH<sub>2</sub>CH<sub>2</sub>Ph, NHNHCH<sub>2</sub>Ph, NHCH<sub>2</sub>Ph(2,4-diF),  
 NHNHPh(2,5-diCl), NHCH<sub>2</sub>Ph(3-F), NHCH(Ph)CH<sub>2</sub>Ph,  
 NHCH<sub>2</sub>Ph(3,4-diOH), NHCH<sub>2</sub>Ph(3,4-diOCH<sub>3</sub>), N(CH<sub>3</sub>)CH<sub>2</sub>Ph,  
 N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>Ph, N(CH<sub>3</sub>)CH(CH<sub>3</sub>)Ph, NHCH<sub>2</sub>CH<sub>2</sub>(3-F)Ph,  
 NHCH(CH<sub>2</sub>Ph)CH<sub>2</sub>OH,

5  $\text{NHCH}(\text{CH}_2\text{Ph})\text{CH}_2\text{OH}$ ,  
 $-\text{N} \text{---} \text{CH}_2\text{CH}_2\text{---} \text{N} \text{---} \text{CH}_2\text{CH}_2\text{---} \text{NH}_2$ ,  $-\text{N} \text{---} \text{CH}_2\text{CH}_2\text{---} \text{NH}_2$ ,  $-\text{N} \text{---} \text{S}$ ,  $-\text{N} \text{---} \text{O}$ ,  
 $\text{N}$  (cyclopentyl),  $\text{N}$  (cyclopentyl)- $\text{CH}_2\text{OH}$ ,  $\text{N}$  (cyclopentyl)- $\text{CH}_2\text{OH}$ ,  $\text{N}$  (cyclopentyl)- $\text{CH}_2\text{OH}$ ,  
 $-\text{N} \text{---} \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{N} \text{---} \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}$  (cyclopentyl)- $\text{S}$ ,  $\text{N}$  (cyclohexyl)- $\text{OH}$ ,  
 $-\text{N} \text{---} \text{OH}$ ,  $-\text{N}$  (cyclohexyl),  $-\text{N} \text{---} \text{CH}_3$ ,  $\text{N}$  (cyclopentyl)- $\text{S} \rightarrow \text{O}$ ,  $-\text{N}$  (cyclohexyl),  
 $-\text{N}$  (cyclohexyl)- $\text{CONH}_2$ ,  $-\text{N}$  (cyclohexyl)- $\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}$  (cycloheptyl),  
10  $-\text{N} \text{---} \text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}$  (cyclooctyl),  $\text{N}$  (bicyclo[4.3.0]nonyl),  $\text{N}$  (1,2,4-triazol-5-yl)- $\text{C}(\text{CH}_3)_2$ ,  
 $-\text{N}$  (cyclohexyl)- $\text{CH}_3$ ,  $-\text{N} \text{---} \text{N} \text{---} \text{C}_6\text{H}_4 \text{---} \text{OCH}_3$ ,  $\text{N}$  (bicyclo[2.2.1]hept-5-yl)- $\text{C}(\text{CH}_3)_3$ ,  
 $\text{NHCH}_2\text{CH}_2 \text{---} \text{C}_6\text{H}_3(\text{OMe})_2$ ,  $\text{PhCH}_2\text{O}_2\text{C} \text{---} \text{N}$  (cyclopentyl),  
 $\text{HN} \text{---} \text{C}_6\text{H}_3\text{O}_2$ ,  $-\text{N} \text{---} \text{N} \text{---} \text{C}_6\text{H}_3\text{O}_2$ ,  $-\text{N}$  (bicyclo[2.2.2]octyl).

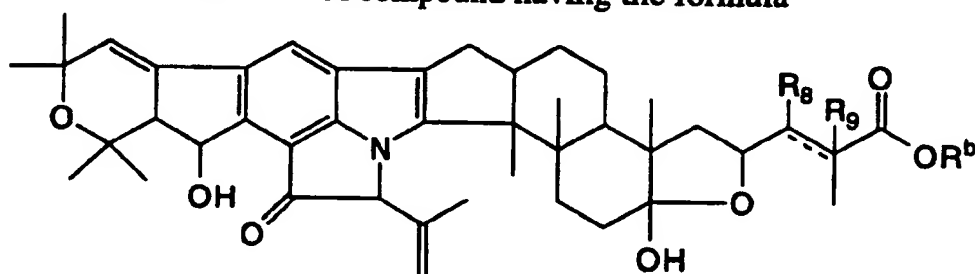




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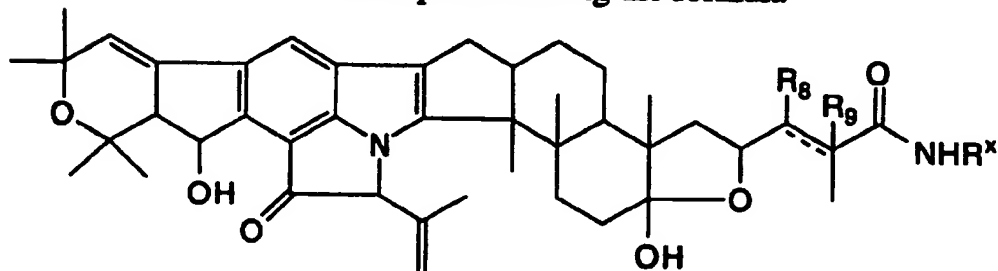


15. A compound having the formula



wherein R<sub>8</sub> and R<sub>9</sub> are hydrogen and separated by a double bond or R<sub>8</sub> is hydroxy, R<sub>9</sub> is hydrogen and separated by a single bond and R<sup>b</sup> is as defined in Claim 12.

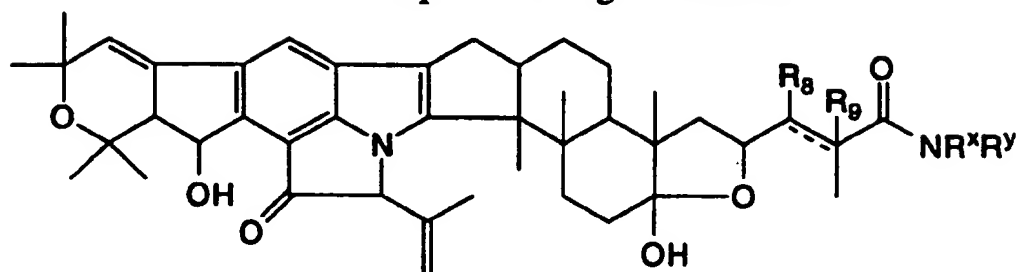
16. A compound having the formula



wherein R<sub>8</sub> and R<sub>9</sub> are hydrogen and separated by a double bond or R<sub>8</sub> is hydroxy, R<sub>9</sub> is hydrogen and separated by a single bond and R<sup>x</sup> is as defined in Claim 13.

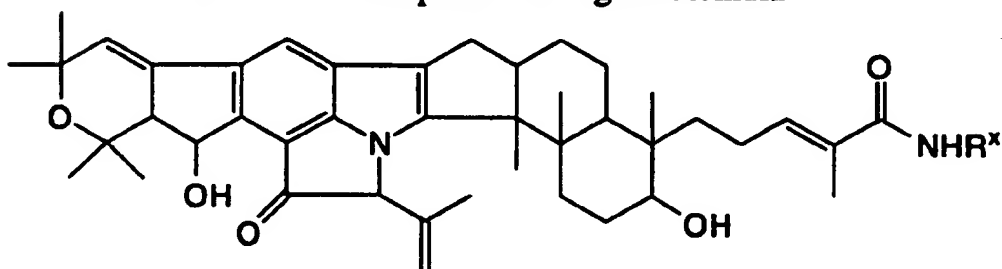
- 117 -

17. A compound having the formula



- 5 wherein R<sub>8</sub> and R<sub>9</sub> are hydrogen and separated by a double bond or R<sub>8</sub> is hydroxy, R<sub>9</sub> is hydrogen and separated by a single bond and NR<sup>x</sup>R<sup>y</sup> is as defined in Claim 14.

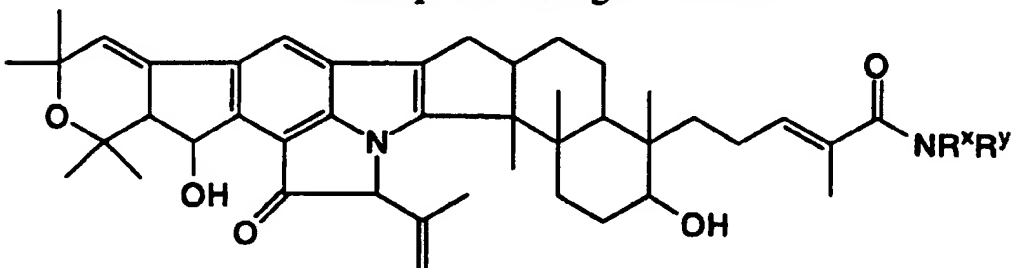
18. A compound having the formula



10

wherein R<sup>x</sup> is as defined in Claim 13.

19. A compound having the formula

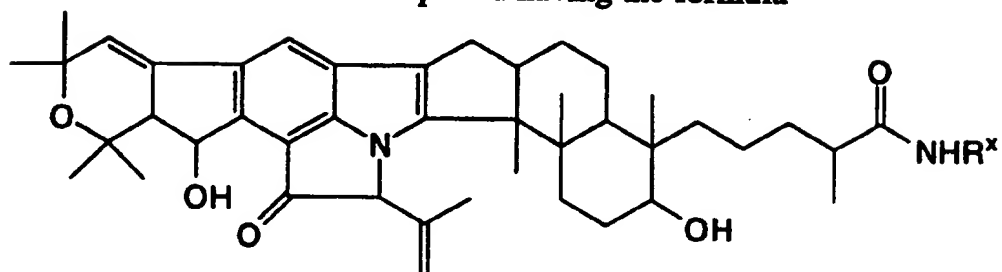


15

wherein NR<sup>x</sup>R<sup>y</sup> is as defined in Claim 14.

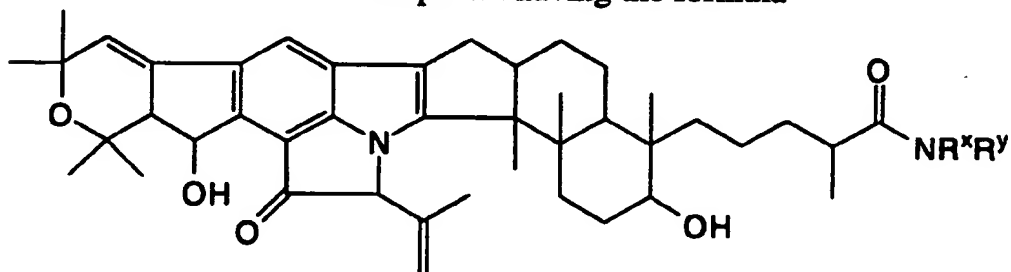
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20. A compound having the formula

wherein  $R^x$  is as defined listed in Claim 13.

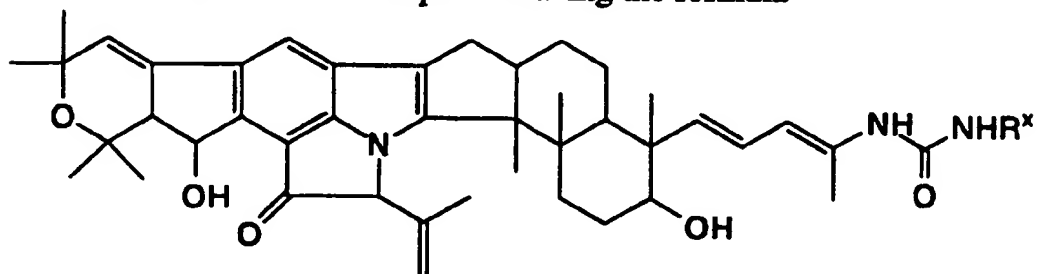
5

21. A compound having the formula

wherein  $NR^xR^y$  is as defined in Claim 14.

10

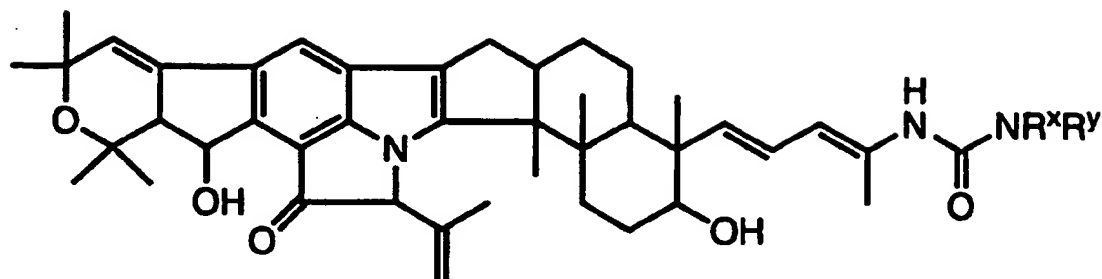
22. A compound having the formula

wherein  $R^x$  is as defined listed in Claim 13.

15

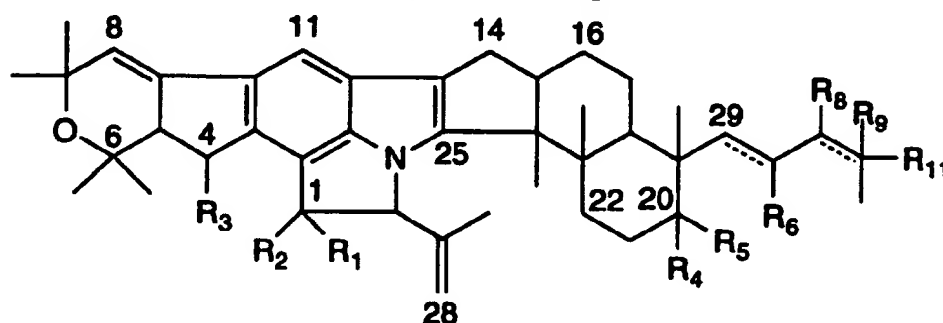
23. A compound having the formula

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wherein NR<sup>x</sup>RY is as defined in Claim 14.

5                    24.           A compound having the formula



where R<sub>1</sub> - R<sub>6</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined in Claim 1;

**R<sub>11</sub> is**

(1)	COCl,
(2)	CON <sub>3</sub> , or
(3)	NCO.

**25. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.**

**26. A composition of Claim 25 further comprising an anthelmintic agent.**

27. A composition of Claim 26 wherein said anthelmintic agent is selected from ivermectin, avermectin, abamectin, emamectin, eprinamectin, doramectin,

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5 fulladectin, moxidectin, Interceptor and nemadectin,  
thiabendazole, cambendazole, parbendazole, oxibendazole,  
mebendazole, flubendazole, fenbendazole, oxfendazole,  
albendazole, cyclobendazole, febantel, thiophanate,  
tetramisole-levamisole, butamisol, pyrantel, pamoate,  
aoxantel or morantel.

10 28. A composition of Claim 25 further comprising  
fipronil, lufenuron or an ecdosyne agonist.

29 A method for treating a parasitic disease in a  
mammal which comprises administering to said mammal an  
antiparasitic effective amount of a compound of Claim 1.

15 30 A method of Claim 29 further comprising  
administering an anthelmintic agent.

20 31. A method of Claim 29 further comprising  
administering fipronil or lufenuron.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/03611

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/40, 31/425, 31/445, 31/495; C07D 405/06, 487/16  
US CL : 514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS Structure

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,399,582 A (A. W. DOMBROWSKI ET AL.) 21 March 1995, columns 1-2, compounds 1-3.	1-3, 5-6, 11-12, 15, 25-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 MAY 1996

Date of mailing of the international search report

20 MAY 1996

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

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